VOL I
FORMIC ACID AND DERIVATIVES #97

VOLUME 1

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FORMIC ACID AND DERIVATIVES

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AND WELFARE

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Table of Contents

BIOCHEMICAL ASPECTS

BIBLIOGRAPHY

JOURNAL ARTICLE COPIES & TRANSLATIONS

SUMMARY

Description

Formic acid is a colorless, highly corrosive, fuming liquid with a sharp, penetrating odor. It is very soluble in water, ethanol, ether, and glycerol.

Ethyl formate is a colorless, unstable liquid with a pleasant peach-like odor and a slightly bitter taste. It is miscible with ethanol, ether, and benzene. It is also slightly soluble in water, but decomposes. Ethyl formate is highly flammable and a dangerous fire and explosion risk.

Sodium formate is a white, deliquescent solid with a slight formic acid odor. It is soluble in water and glycerol, slightly soluble in ethanol, but insoluble in ether.

Occurrence

Formic acid occurs naturally in the poison of ants, wasps, bees, and some other insects. It is a normal constituent of mammalian muscle tissue, sweat, and urine. A number of plants such as nettles, unripe grapes, peaches, raspberries, etc. also contain formic acid. Relatively large amounts are formed when coffee is roasted. Formic acid is present also in wines, rum, and certain other distilled fermented fruit beverages. It is found in some mineral waters. Reported natural concentrations range from 2 to 770 mg per 100 grams.

Ethyl formate is found naturally in a variety of plant oils, fruits, and juices such as oranges, apples, pears, and in honey. It is present also in wines, rum, and certain other distilled liquors. Apparently it does not occur naturally in the animal kingdom. In the food industry, ethyl formate is used as a flavoring in candy,

chewing gum, ice cream, baked goods, etc., and in many essences. It is used also as a fumigant for certain dried fruits, nuts, cereals, and tobacco. (018,139,491). Possible daily intake values range from 1 to 84 mg approximately.

Formic acid and sodium formate are included in the category of substances possibly migrating to foods from paper and paperboard food containers, where they are used in manufacturing processes.

Acute Toxicity

Formic acid in mice has an oral LD_{50} values of 1100 mg/kg BW (275), 940 mg/kg via the peritoneum (435), and 145 mg/kg when injected intravenously (275); when administered intrarectally, the lethal dose is 1250 mg/kg BW (491). In rats, the oral LD_{50} is 1830 mg/kg BW (435); in rabbits the oral MLD is greater than 4000 mg/kg (491) while the intravenous MLD is 239 mg/kg (433). For daphnias and fish, the LD_{50} values are 70 and 175 mg/liter, respectively (109,435).

Ethyl formate has an oral LD_{50} of 1850 mg/kg BW in rats (217) and a value of 1110 mg/kg in guinea pigs (217). By inhalation, the fatal dose is 24 mg/liter in rats (429) and 32 mg/liter in cats (491).

Sodium formate has an oral LD_{50} of 11,200 mg/kg BW in mice (275) and an MLD of 4000 mg/kg in dogs (420). In mice, by the intravenous route, the LD_{50} is 807 mg/kg (275); in dogs the MLD is 3000 mg/kg (430). For fish, the LD_{50} is 5000 mg/liter by immersion (109).

Short-term studies

Formic acid is reported to have caused anemia, leucopenia, basophile neutropenia, and a slight lymphocytosis in rats when given at a level of 1% in the drinking water. The offspring mortality rate also was stated to be high (425). In another study, formic acid at a level of 360 mg/kg BW daily for 9 weeks, after 90 mg/kg BW daily for

17 weeks, depressed food intake and retarded growth (430). Weanling rats fed diets containing ethyl formate as high as 10,000 ppm for 17 weeks grew normally and remained in good health throughout. Hematologic findings were normal and no gross or microscopic abnormalities were detected (173).

Guinea pigs and rabbits exposed to ethyl formate in the atmosphere at levels of 40 to 130 mg per liter suffered marked central nervous system depression (260). On the other hand, doses as large as 1000 mg/kg BW subcutaneously were tolerated without any evidence of toxicity (260,491). Silage containing formic acid at a level of 1/2 gallon per ton, fed to cattle for 12 weeks, apparently caused no harmful effects (074).

In man, massive doses of sodium formate (2-3 grams several times a day) caused vertigo, nausea, vomiting, albuminuria, hematuria, vesical tenesmus, dyspnea, and lowered temperature (445). A single dose of 3-4 grams caused albuminuria and hematuria in one of three subjects but the condition cleared up after five days (491). Daily doses of 150 mg/kg BW per os for some time caused no harm (430). A single dose of 4 grams intravenously was tolerated without signs of toxicity (491). Formic acid in 500 mg amounts in lemonade given daily for 4 weeks caused no harmful effects (491). Larger doses produced irritation of the gastrointestinal tract followed by vomiting and diarrhea (491).

Formic acid and formates are quite toxic via the respiratory tract. Inhalation of concentrations as low as 32 mg per liter by human subjects caused progressive irritation of the eye and mucous membranes which persisted for as long as four hours (491). Locally, formic acid is corrosive to the skin and mucous membranes. Even mild exposures may be followed by severe after-effects (491).

Long-term Studies

Rats tolerated sodium formate at a level of 730 mg/kg BW daily in the drinking water for 1.5 years without evidence of toxic effects (275).

Special Studies

Formic acid at a level of 0.1% caused mutation in Drosophila melanogaster (450). In concentrations as low as 0.005%, it induced mutation in Eschericha coli from streptomycin-dependence to non-dependence (097).

Doses of sodium formates as high as 20 mg per egg were not toxic or teratogenic for chick embryos (275).

No statistically significant evidence of histologic abnormalities were detected in the skin of mice painted with 8% formic acid for a period of 50 days (142).

Biochemistry

Formic acid and sodium formate are rapidly absorbed from the stomach. Formic acid is absorbed also through the intact skin and via the lungs. Ethyl formate is absorbed through the lungs as well as from the gastrointestinal tract (271,491).

Absorbed formic acid or formate apparently is partly oxidized, partly excreted unchanged in the urine, and partly metabolized in the tissues. The liver appears to be the main site of formate oxidation (491). The oxidation mechanism, in the rat at least, involves a catalase-hydrogen peroxide complex and the enzymes responsible for peroxide formation (331). Folic acid and vitamin B_{12} are essential for normal formate oxidation (197,320). Small doses of formic acid administered to experimental animals are usually oxidized almost completely whereas 50% or more of larger doses are excreted unchanged in the urine (491). The biological half-life varies according to the species, from 12 minutes in the rat to 77 minutes in dogs. Values of 45-46 minutes have been obtained with human subjects (275,277).

Formic acid is a normal constituent of human urine and individuals on a mixed diet excrete from 13 to 120 mg daily (156,277). The fate of ethyl formate in the body apparently has not been determined (491).

The participation of the formate ion in intermediary metabolism is well-established (011,156). Retained formate is rapidly utilized in the formation of protein, lipids, carbohydrates, and nucleic acids and these in turn are distributed throughout all tissues of the body (370,434). Formate is a precursor, through one-carbon metabolism, of serine, methionine, cysteine, and purines; it ultimately becomes incorporated through these precursors into proteins and nucleic acids (370). Formate is incorporated also into carbohydrates via glucose and the glucogenic amino acid serine (011).

Normally, only small amounts of formate are ingested in foods but many compounds contribute to the C_1 pool for formation of endogenous formate; among these are serine, glycine, histidine, methionine, choline, sarcosine, and acetone (056).

Folic acid, vitamin E, and ascorbic acid are involved in control of formate metabolism; deficiencies in any of these cause metabolic derangement (105,197,320).

The nervous system appears to be especially susceptible to the action of formates. Small doses cause depression; large amounts cause convulsions, paralysis of the medulla, and death (491).

Heart action is stimulated by trace amounts (1 ppm) of formic acid. Concentrations as low as 1:10,000, however, quickly and irreversibly stop heart action. Symptoms of cardiac injury are increase and then decrease of the systole, slowing of the heart beat, contraction irregularities, arrhythmias, and diastole arrest (491).

Formic acid intravenously causes immediate vasoconstriction. Sodium formate, on the other hand, causes vasodilation in the liver, brain, and kidney, but vasoconstriction in the limbs (491).

Gastric secretion and peristalsis are stimulated by formic acid. There is also a diuretic effect. Single large doses or repeated small doses cause kidney damage (491).

Formic acid inhibits lysozyme, ribonuclease, and trypsin (425). Small doses cause a persistent methemoglobinuria apparently due to action on catalase.

Formic acid is reported to have strong germicidal properties (491) and has been used as a food preservative in certain European countries (137). Germicidal action is believed to reside in the un-ionized molecule (491). Methyl, ethyl, and isopropyl formates were effective against various life cycle stages of the dried fruit beetle, raisin moth, and other insects that infest dried fruits, nuts, cereals, and tobacco. They are used as fumigants in these areas of the food industry (018,139,485,491).

Folic acid antagonist drugs such as methotrexate inhibit metabolism of formic acid, resulting in increased excretion of it in the urine (275).

Consumer Exposure

Formic acid is found in a number of plants, fruits, fruit juices, and wines as well as in milk, meats, certain vegetables, and some mineral waters (056,146,275). In the food industry, formic acid is used to a limited extent as a flavor adjunct in candy, ices, ice cream, baked goods and several other food categories (146).

Ethyl formate occurs naturally in certain fruits, fruit juices, wines, rum, and some other distilled alcoholic beverages (146). It is a component of a number of food flavorings and is used in chewing gum, candy, ice cream,

ices, baked goods, and several other food categories (39). Maximum daily intakes up to 84 mg have been reported (138). Ethyl formate is used also as a bulk and package fumigant for certain dried fruits, nuts, cereals, and tobacco (018,139,491). With raisins and dried Zante currants, the maximum concentration permitted in the final product is 250 ppm (018).

Formic acid and sodium formate are included in the category of substances possibly migrating to foods from paper and paperboard food containers that employ formates in their manufacture (019).

Safe levels

Acceptable daily intake levels for formic acid and ethyl formate are 0-5 mg/kg body weight, for each, calculated as total formic acid and from all food additive sources. Maximum allowable concentrations per 8-hour work shift are 9 mg per cubic meter of air for ethyl formate (016,515,516).

CHEMICAL INFORMATION

I. Nomenclature

A. Common name:

Formic acid:	Formic acid; Methanoic acid; Hydrogen carboxylic acid
Ethyl formate:	Ethyl formate; Formic ether; Ethyl methanoate
Sodium formate:	Sodium formate

B. Chemical name

Formic acid:	Formic acid
Ethyl formate:	Formic acid, ethyl ester
Sodium formate:	Formic acid, sodium salt

C. Trade names:

Formic acid:	Formisoton; Acirufan; Formidium (Therapeutic preparations)

D. Chemical Abstracts Services Unique Registry Number:

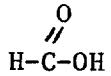
Formic acid:	64186
Ethyl formate:	109944
Sodium formate:	141537

II. Empirical formula

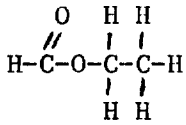
Formic acid:	HCO_2H
Ethyl formate:	$HCO_2C_2H_5$
Sodium formate:	$NaCHO_2$

III. Structural formula

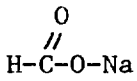
Formic acid:



Ethyl formate:



Sodium formate:



IV. Molecular Weight

Formic acid:	46.03
Ethyl formate:	74.08
Sodium formate:	68.01

V. Specifications

The Food Chemicals Codex (088) lists the following specifications for food-grade formic acid and ethyl formate.

Formic acid

Assay - not less than 85 percent of CH_2O_2

Dilution test - passes test.

Limits of impurities

Acetic acid - not more than 0.4 percent

Arsenic (as AS) - not more than 3 ppm (0.0003%)

Heavy metals (as Pb) - not more than 10 ppm (0.001%)

Sulfate - not more than 40 ppm (0.004%)

Ethyl formate

Assay - not less than 95 percent $C_3H_6O_2$

Refractive index - between 1.359 and 1.363 at 20°C.

Solubility in alcohol - passes test

Specific gravity - between 0.916 and 0.921

Limits of impurity

Free acid (as formic acid) - not more than 0.1%

Arsenic (as As) - not more than 3 ppm (0.0003%)

Heavy metals (as Pb) - not more than 10 ppm (0.001%)

Sulfate - not more than 40 ppm (0.004%)

VI. Description

A. Formic acid - a colorless, highly corrosive, fuming liquid with a pungent, penetrating odor.

Physical constants:

Solubility: Completely miscible with water, ethanol, ether, and glycerol.

Specific gravity: 1.2201

Refractive index: 1.3719

Melting point: 8.3°C

Boiling point: 100.8°C

Flash point: 156°F.

Autoignition temperature: 1114°F.

May deteriorate in normal storage causing a hazard.

B. Ethyl formate - a colorless, unstable liquid with a pleasant, peach-like odor and a slightly bitter taste.

Physical constants:

Solubility:	Miscible with ethanol, ether, and benzene. Slightly soluble in water but decomposes.
Refractive index:	1.35975
Melting point:	-80.5°C.
Boiling point:	-54.3°C.
Blash point:	-4°F.
Autoignition temperature:	851°F.

Is highly flammable and a dangerous fire and explosion risk.

C. Sodium formate - a white, deliquescent solid with a slight formic acid odor.

Physical constants:

Solubility:	Soluble in water (1:13 RT) and glycerol; slightly soluble in ethanol; insoluble in ether.
Specific gravity:	1.92
Melting point:	253°C.

Is deliquescent; containers must be tightly closed.

VII. Analytical Methods

A. The Association of Official Agricultural Chemists (AOAC) has presented a steam distillation method for the extraction of volatile fatty acids from a sample (027). The apparatus used is shown in Figure 1. Any similar distillation assembly can be used if it is designed to handle the same volumes as the AOAC assembly, and 57 $\pm$ 2% recovery of acetic acid is obtained upon distillation.

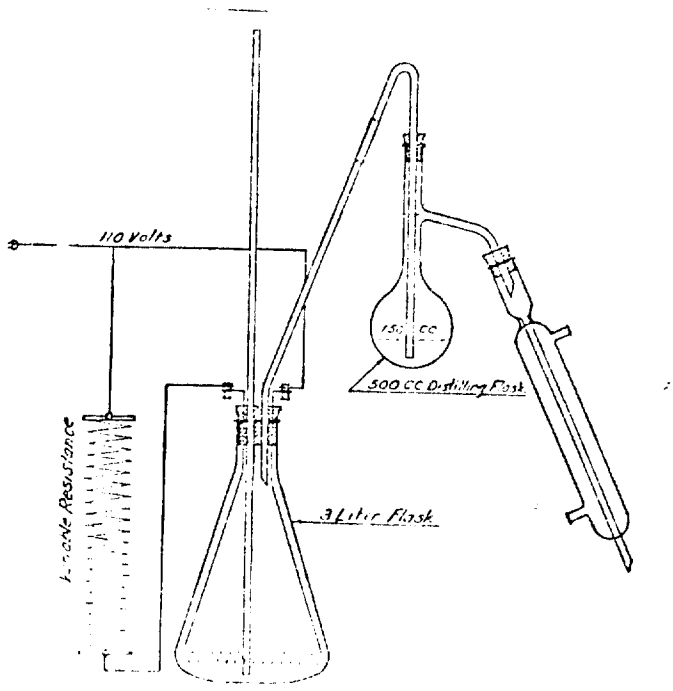


Figure 1. Steam Distillation Assembly of the AOAC (027)

B. Formic acid may be detected by formation of derivatives. The melting points of some characteristic derivatives are given in Table 1. Similar derivatives of other volatile fatty acids are included for comparison (080).

Table 1. Derivatives of Some Volatile Fatty Acids and Their Melting Points (080).

Acid	B.P. (°C)	M.P.(°C)	Derivatives and melting points p-toluidide	anilide	p-bromo-phenacyl ester	p-nitro-benzyl ester
Formic	100.7	8.4	53	50	140;135	31
Acetic	118.2	16.6	153;147	114	86.0	78
Propionic	141	-20.8	126;123	106	63.4	31
n-Butyric	162.5; 164	-5.5; -8	75	96;97	63	35
n-Pentanoic	186.4	-34.5	74	63	75	---

C. When formic acid is present as the only source of acidity in the sample, or when other acids are present in negligible amounts, a standard alkaline titration will suffice to measure the formic acid content. Titration with 0.05 N NaOH to a phenolphthalein end-point is a standard method (015).

D. Where other acids which do not react readily with permanganate are present, a redox titration may be used for formic acid determination (015). The formic acid solution is made alkaline with sodium carbonate and permanganate is added. The solution is acidified, an excess of oxalic acid is added, and a back titration performed. The redox titration may also be performed by adding excess permangante to the alkaline sample and heating to 70°C. A sufficient amount of KI solution is added, followed by a back-titration using standard $Na_2S_2O_3$ (thiosulfate) (015).

E. Formic acid may be determined in the presence of other acids (notably acetic acid) by its reduction of soluble mercury (II)chloride, $HgCl_2$ to insoluble mercury(I)chloride, Hg_2Cl_2. The reaction requires two hours of heating under a reflux condenser. The mercury is filtered and dried, and the weight used to calculate formic acid content of the original sample (015). This method is also presented by the AOAC for formic acid determination following steam distillation of the sample (027,028).

F. Shelley, et al. (420) have presented a method for the quantitative measurement of formic acid and other volatile fatty acids by gas chromatography. The method employs methyl enanthoate as an internal standard. Recoveries ranged from 95-105% for lower concentrations of acids and 97-101% for higher concentrations. The method was compared to the "Official" AOAC method (reduction of mercury(II)chloride, above) and good agreement was found. The gas chromatographic method was found to be more sensitive to the lower concentrations of acids. AOAC methods (028) included a gas chromatographic method for formic acid and the other volatile fatty acids similar to the method of Shelley, et al.

Watson and Crescuolo (603) found that microgram and sub-microgram quantities of formic, acetic, and propionic acids may be determined by gas chromatography as the p-substituted benzyl esters. Optimum results were realized with p-bromobenzyl derivatives. Table 2 shows the retention time of the various p- substituted benzyl esters; Fig. 2 is a chromatograph of a micro preparation of the p-bromobenzyl esters.

Table 2. Retention Times (min) of p-substituted Benzyl Formate Acetate and Propionate Esters and Other Relevant Related Compounds (503)

	p-Methylbenzyl (column temp. 100°)	p-Bromobenzyl (column temp. 120°)	p-Nitrobenzyl (column temp. 145°)
Formate	8.4	10.9	11.0
Acetate	15.1	17.0	15.3
Propionate	26.3	27.4	22.8
Alcohol	6.6	10.2	12.6
Halide	9.3	12.7	25.5
Artifact	5.7	7.5	7.2

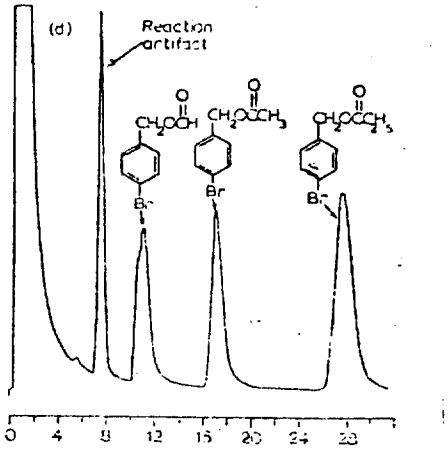


Figure 2. Chromatograph of p-Bromobenzyl Ester Reaction Mixture (micro preparation using three-component acid solution (503).

VIII. Occurrence and Levels

A. Formic acid

Formic acid occurs in the poison of ants (Formicidae), bees, wasps, stinging caterpillars, etc. and is partly responsible for its irritant effects. It was discovered in 1670 by distilling red ants (Formica rufa) with water. Bees impart some of their formic acid to the honey. Certain of the Isopoda contain formic acid and have diuretic properties (445). Formic acid is also a normal constituent of mammalian muscle tissue, sweat, and urine (275).

A number of plants contain formic acid. Nettles, Douglas fir needles, unripe grapes, petitgrain lemons, peaches, raspberries, strawberries, mace oil, valerian root extract, and bitter orange are typical examples (139,146). Relatively large amounts are formed when coffee is roasted and this is concentrated in coffee extracts (146). Formic acid is present also in rum, wines, and certain other distilled fermented fruit beverages. It is found in some mineral waters (156).

Formic acid is used to a certain extent industrially. It is a rubber latex coagulant, a decalcifier, reducer in dyeing and finishing of textiles and paper, and a constituent of certain sizes (438). It is used in dehairing and plumping hides, tanning, reclaiming old rubber, ore flotation, and electroplating (146). In the food industry, it is used as a flavoring adjunct, animal feed additive, brewing antiseptic, and, in certain European countries, as a food preservative (137,146,156). Levels found in some common foods and beverages are shown in Table 3.

Table 3. Formic Acid Content Reported for Some Common Foods and Beverages

Food	Amount Formic Acid (mg/100g)	Reference
Fruits	2-4	414
Fruit juices	3-10	501
Fruit syrups	65-163	406
Honey	2-200	128
Wines	0.1-34	464,475
Coffee, roasted	135-220	098
Coffee extracts	200-770	098
Milk (evap.)	3-4	295
Cheese	2-30	210,255

B. Ethyl formate

Ethyl formate is found in a variety of plant fruits and oils. Oranges, apples, pears, honey, and the oil of Boronia dentigeroides, are typical examples. It is present also in wines and certain distilled liquors such as rum (146).

No reports were found of its presence in the animal kingdom.

Ethyl formate is used industrially in the manufacture of cellulose acetate and nitrate and as a solvent for oils, fats, and waxes. In the food industry, it is used as a flavoring agent and as a fumigant (fungicide and larvacide for certain dried fruits, nuts, cereals, and tobacco (018,139,491).

C. Sodium formate

No information was found concerning the occurrence of sodium formate in plants or animals. Commercially, it is used in adhesives, as a reducing agent, as a mordant, in the dyeing and printing of fabrics, and in tanning. Chemically, it is used as a buffer and as a solubilizer for trivalent metallic ions.

BIOLOGICAL DATA

I. Acute Toxicity

A. Fish

Dowden et al (109) exposed Bluegills (number, age, sex, weight not given) to graded amounts of formic acid or sodium formate in an organic-free medium for a period of 24 hours and determined the median tolerance (TLm), i.e., the minimum concentration lethal to 50% of the fish within the 24 hour exposure period. The results are given in Table 4.

B. Daphnias

Sporn et al (435) subjected Daphnias to varying levels of formic acid in a nutrient medium over a period of 48 hours. (See Table 4.)

C. Mice

1. Sporn et al (435) injected white mice (number, age, weight, sex, and strain not given) intraperitoneally with varying amounts of formic acid in an acute toxicity study. (See Table 4.)

2. Malorny (275) determined the oral and intravenous LD_{50} values for formic acid and several of its salts (see Tables 4 and 5) with white mice (age, weight, sex, and strain not specified), employing 45 to 55 animals for each compound.

D. Rats

1. Jenner, Fitzhugh et al. (217) determined the oral (by intubation) LD_{50} value for ethyl formate in young adult Osborne-Mendel rats, 10 per group evenly divided by sex, after a fasting period of 18 hours. Water was accessible at all times. Food was returned after administration of the compound. The animals were closely observed for toxic symptoms and the time of death recorded for all fatalities. Observations were continued until the survivors appeared normal and showed weight gain. The data are represented in Tables 4 and 6.

2. Sporn et al. (435) determined the oral LD_{50} (see table 4) of formic acid in young white rats (number, weight, sex, and strain not specified). Dyspnea and cyanosis preceded death. Weakness and diarrhea with a slow return to normal was characteristic of the survivors.

3. Smyth et al. (429) exposed rats, six per group, (strain, age, sex, and weight not given), to ethyl formate vapor of varying concentrations for a period of four hours and recorded the fatalities over a 14-day observation period. The results are summarized in Table 4.

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Table 4. Acute Toxicity of Formic Acid, Ethyl Formate, and Sodium Formate

Substance	Animal	Sex & No.	Route	Dosage mg/kg	Measurement	Reference/ Bibliography No.
Formic Acid	Fish	-	Immersion	175[a]	LD_{50}	Dowden (109)
Formic Acid	Daphnias	-	Immersion	70[a]	LD_{50}	Sporn (435)
Formic Acid	Mice	-	p.o.	1100	LD_{50}	Malorny (275)
Formic Acid	Mice	-	i.v.	145	LD_{50}	Malorny (275)
Formic Acid	Mice	-	i.p.	940	LD_{50}	Sporn (435)
Formic Acid	Mice	-	i.r.	1250	LD	von Oettingen (491)
Formic Acid	Rats	-	p.o.	1830	LD_{50}	Sporn (435)
Formic Acid	Rabbits	-	p.o.	4000+	MLD	von Oettingen (491)
Formic Acid	Rabbits	-	i.v.	239	MLD	Spector (433)
Ethyl Formate	Rats	-	p.o.	1850	LD_{50}	Jenner (217)
Ethyl Formate	Rats	-	Inhalation	24[a]	FD	Smyth (429)
Ethyl Formate	Guinea pigs	-	p.o.	1110	LD_{50}	Jenner (217)
Ethyl Formate	Cats	-	Inhalation	32[a]	LD	von Oettingen (491)

[a] mg/liter

Table 4. (Continued)

Substance	Animal	Sex & No.	Route	Dosage mg/kg	Measurement	Reference Bibliography No.
Sodium Formate	Fish	-	Immersion	5000[a]	LD_{50}	Dowden (109)
Sodium Formate	Mice	-	p.o.	11,200	LD_{50}	Malorny (275)
Sodium Formate	Mice	-	i.v.	807	LD_{50}	Malorny (279)
Sodium Formate	Dogs	-	p.o.	4000	MLD	Sollmann (430)
Sodium Formate	Dogs	-	i.v.	3000	MLD	Sollmann (430)

[a] mg/liter

Table 5. LD_{50} Formic Acid and its Salts (Mouse) (275)

Substance	LD_{50} mg/kg	LD_{50} Range mg/kg	Calculated according to formate	Number of animals
Per os				
Formic acid	1100	1000-1200	1076	55
Sodium formate	11200	9600-12800	7410	45
Potassium formate	5500	5000-6000	2950	50
Ammonium formate	2250	2050-2460		
Calcium formate	1920	1280-2560	1330	45
Intravenous				
Formic acid	145	138-151	142	50
Sodium formate	807	800-813	534	50
Potassium formate	95	93-97	51	55
Ammonium formate	410	408-412	293	50
Calcium formate	154	150-158	107	55

Table 6. Acute Oral Toxicity of Ethyl Formate (217)

Animal	LD_{50} (mg/kg)	Slope function	Toxic signs and death times (D.T)
Rat	1850 (1520-2240)[a]	1.6 (1.3-1.9)[a]	Depression within 5-10 minutes. Labored respiration. D.T. 15 min-2 hr.
Guinea pig	1110 [a] (887-1390)	2.0 (1.3-3.1)[a]	Depression. Irritated gastrointestinal tract. D.T. 10 min-2 hr.

[a] 95% confidence limits

E. Guinea Pigs

1. Jenner, Fitzhugh et al. (217) administered varying doses of ethyl formate to groups of young guinea pigs consisting of males and females, by intubation, after a fasting period of 18 hours. The animals were then given free access to food and water, and closely observed for signs of toxicity. The time of death was recorded for all fatalities and observation continued until survivors appeared normal and gained weight. The LD_{50} value, slope function and their confidence limits along with toxic symptoms and death times are given in Tables 4 and 6.

2. von Oettingen (491) reported that according to Duquenois and Revel, inhalation by guinea pigs of air saturated with ethyl formate vapors "resulted within a few minutes in tremors, progressive depression of the central nervous system, and death from circulatory and respiratory failure."

F. Cats

Flury and Neuman (260) exposed cats (number, strain, age, weight and sex not specified) to several concentrations of ethyl formate vapor in air for varying periods of time. The animals were then closely observed for toxic signs and the time of death recorded for all fatalities (see Table 4).

Concentrations as low as 32 mg/liter for 20 minutes caused moderate irritation of the mucous membranes of the eye and respiratory tract. Progressive narcosis resulted after 80 minutes, and death with pulmonary edema followed an exposure period of 90 minutes.

A concentration of 44 mg/liter caused marked irritation of the mucous membranes, severe dyspnea, and staggering after 17 minutes. When the exposure time was increased to 20 minutes and then discontinued, one of the two animals recovered but the other died from pulmonary edema.

G. Dogs

1. von Oettingen (491), reporting an early study by Fleig, states that the fatal dose of 4000 mg/kg BW of formic acid for the dog per os causes repeated vomiting, clonic convulsions, progressive dyspnea prior to death by respiratory paralysis.

2. Stern (445) reports that formic acid diminishes heart action and blood pressure. The fatal dose was 1000 mg/kg BW (route not specified). Death was due to cardiac paralysis.

H. Human Toxicity

Reviews and surveys indicate that severe and fatal cases of formic acid poisoning in man are not unusual (491). Thirty-four cases were reported over an eight-year period in Travancore, the largest rubber-producing area in India, where the acid is extensively used for the coagulation of latex. Twenty-seven fatalities were suicidal, six accidental, and one due to an over-dose. Although the minimum amount ingested in these cases was not available, two ounces of the concentrated acid were always fatal. Quantities detected in the victims ranged from 0.04 to 31.8 grams (anhydrous acid) (222).

The signs and symptoms of fatal formic acid poisoning in man are: salivation, burning sensation in the mouth and pharynx, agonizing pain, bloody vomitus, and diarrhea. The pulse and respiration are rapid and soft at first but then slow down. The skin becomes cold and clammy, blood pressure drops and shock ensues. There is respiratory distress, cyanosis, and death may follow within 48 hours. Some patients develop albuminuria (with casts), hematuria, subsequent anuria, and may die from uremia, circulatory failure, or pneumonia (491).

Pathologic changes after ingestion of formic acid are similar to those of other corrosive acids. The tongue, palate, pharynx, and esophagus become hyperemic, swollen, and covered with necrotic spots. The larynx and trachea may be edematous and inflammed with hemorrhages. Stomach walls may be edematous with necrotic areas and contain bloody material or they may be dry and brittle. The jejunum is usually like the stomach but less severe. The kidneys are hyperemic and may be hemorrhaged and resemble the state in nephritis. The liver may show hemosiderin deposits (491).

The minimum fatal dose of formic acid and ethyl formate for man by mouth is estimated to be 30 grams or approximately 500 mg/kg BW (433). Sodium formate is less toxic with estimates ranging from 1000 to 4000 mg/kg BW orally. (155,430). The formate ion, however, may have a direct action on the brain in sublethal concentrations (491). Methemoglobinemia also has been detected in experimental animals (491). Formic acid and ethyl formate are toxic via the respiratory tract also and maximum allowable concentrations for eight hours of exposure daily are nine and 300 mg per cubic meter of air, respectively (016).

II. Short-term Studies

A. Yeasts

Watts (504) studied the action of formic acid, methanol, and formaldehyde on the oxidation of glucose, succinate, and ascorbate by yeast and rat liver slices and homogenates in an effort to shed light on the mechanism of methanol poisoning. Conventional Warburg manometric techniques were used. Results are shown in Fig. 3 and Tables 7 and 8.

Various enzymes were inhibited (3-10%) by formic acid at a level as low as 0.005M (Table 8). Tissue respiration was depressed 50% by concentrations as low as 0.04 to 0.16M (Table 7 and Fig. 3). These concentrations approximate the level found in tissues during fatal methanol poisoning in the rabbit with the minimum lethal dose. Further study showed, however, that formaldehyde (another tissue oxidation product of methanol) was ten times as potent as formic acid as a respiration inhibitor. The author concluded, therefore, that the former was more likely the main toxic factor in methanol poisoning rather than formic acid which had been postulated.

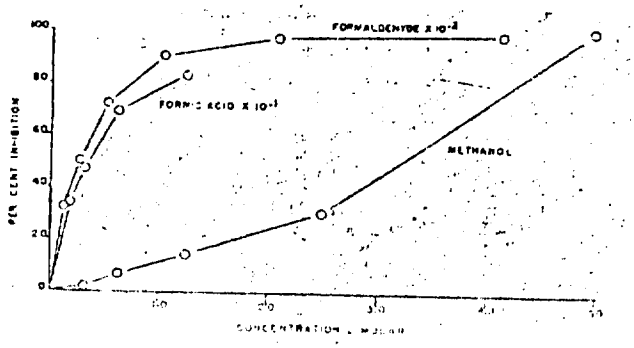

Fig. 3 The Inhibition of Oxidation of Succinate by Rat Liver Homogenate by Increasing Concentrations of Methanol, Formaldehyde, and Formic Acid (504).

Table 7. Concentration of Methanol, Formaldehyde, and Formic Acid Required to Produce 50% Inhibition of Tissue Respiration (504)

Tissue	Substrate and activity measured	Concentration Methanol *M*	Formaldehyde *M*	Formic acid *M*
Yeast	Glucose oxidation	>1.5	0.003	0.32
Yeast	Glucose fermentation	>1.0	0.003	0.16
Liver slices	Glucose oxidation	>1.0	0.010	0.50
Liver homogenate	Succinate oxidation	3.2	0.003	0.04
Liver homogenate	Ascorbate oxidation	>1.5	0.010	0.07

Table 8. The Comparative Inhibition of Tissue Respiration by 0.005 M Methanol, Formaldehyde and Formic Acid (504)

Tissue[a] and determination	Substrate	Control mm.[3] gas, mean ± s.e.	Change from control Methanol %	Formaldehyde %	Formic acid %
Yeast, $Q_{CO_2}^{N_2}$ (wet weight)	Glucose	79.0 ± 2.4	+0.09	−56.6[b]	+10.1
Yeast, $Q_{O_2}^{air}$ (wet weight)	Glucose	20.3 ± 0.5	−9.9	−67.3[b]	−5.1[c]
Liver slices, $Q_{O_2}^{O_2}$ (wet weight)	Glucose	1.47 ± 0.07	−0.7	−39.8[b]	−8.2
Liver homogenate $Q_{O_2}^{air}$ (wet weight)	Succinate	25.6 ± 0.5	−6.6	−60.5[b]	−10.3[c]
Liver homogenate $Q_{O_2}^{air}$ (wet weight)	Ascorbate	15.7 ± 1.4	−1.3	−24.8[b]	−3.2

[a] Additions to Warburg vessels:

(*a*) Five milligrams of yeast was suspended in 2 ml. of 0.02 *M* KH_2PO_4 (pH 4.8) to which was added 1 ml. of 3% glucose. Temperature 30°C.

(*b*) Liver slices were suspended in Krebs-Ringer phosphate containing 0.3% glucose. Temperature 37°C.

(*c*) With minor modifications the homogenate method as described by Potter (8) was used for the oxidation of succinate and ascorbate.

(*d*) The final volume in all vessels was 3.0 ml. plus 0.2 ml. 20% KOH in center well for oxygen uptake measurements. Formic acid was adjusted to the pH of the suspension media before adding it to the vessels.

[b] Statistical analysis of the data gave *P* values of less than 0.001 for these changes; this indicates the inhibition is highly significant.

[c] *P* values for these changes were less than 0.05 which indicates they are probably significant changes. *P* values for all the other changes were greater than 0.05, and hence are not significant.

B. Rats

1. Hagan, Fitzhugh et al.(173) studied the oral subacute toxicity of ethyl formate in the rat in an investigation involving a large number of food flavorings and compounds of related structure.

Twenty weanling Osborne-Mendel rats (10 males and 10 females), litter mates, randomized by weight (same weight at each level), were fed diets containing ethyl formate at levels of 1000, 2500, and 10,000 ppm for a period of 17 weeks. A control group of the same number was maintained on the basic diet alone.

Food intake, body weight, and general condition were recorded each week. Fatalities were autopsied, tissues examined for gross pathologic changes, and suspected cause of death recorded; the vital organs were preserved for microscopic study, if not too far autolyzed. Hematologic studies (white cell counts, red cell counts, hemoglobin, and hematocrits) were made at the end of the study. The animals were then sacrificed and all tissues examined macroscopically. Also, liver, kidneys, spleen, heart, and testes were weighed and preserved in 10% buffered formalin-saline, along with the remaining abdominal and thoracic viscera, for histopathologic examination. A detailed microscopic examination of the tissues of six to eight rats (same number of each sex) from the 10,000 ppm group was made.

All animals survived the 17-week feeding period without manifestations of toxic effects or growth retardation. Hematologic findings were normal. No gross or microscopic abnormalities were noted in any of the organs or tissue sections studied.

2. Sporn et al. (435) conducted a chronic toxicity study in rats with formic acid administered in the diet or in the drinking water for varying periods of time.

In the first experiment, young white rats, 40-41 grams BW, eight animals per group, were fed a casein diet containing formic acid at levels of 0.5% or 1.0% for a period of five to six weeks to determine effect on growth. The amount of food ingested, weight gain, and protein efficiency were determined. The results are presented in Table 9. Growth was retarded at both levels of formic acid but the authors state that the degree was not significant statistically.

Table 9. Influence of Formic Acid on the ... th of White Rats (435)
Mean Data Per Group

Group	Initial Indicator	Week						Mean Totals
		I	II	III	IV	V	VI	
I. Casein Control 18.2%	Weight 40.1	56.8	79.0	96.3	116.9	131.9	-	
	Ingestion	49.1	63.6	77.8	85.4	85.0	-	360.8
	Protein Efficiency	1.86	1.91	1.22	1.32	0.96	-	1.39
II. Formic Acid 0.5%	Weight 40.5	58.6	77.6	90.3	105.3	120.9	-	
	Ingestion	46.0	63.9	69.9	80.0	83.1	-	342.9
	Protein Efficiency	2.16	1.63	0.99	1.33	1.03	-	1.28
III. Formic Acid 1%	Weight 40.6	60.3	80.7	100.6	117.6	131.0	-	
	Ingestion	48.9	69.0	80.1	83.3	86.6	-	367.9
	Protein Efficiency	2.20	1.62	1.36	1.12	0.90	-	1.36
IV. Casein Control 11.8%	Weight 40.1	53.5	64.1	75.3	93.5	107.0	115.8	
	Ingestion	53.9	62.0	71.6	81.0	76.4	71.3	416.2
	Protein Efficiency	2.10	1.58	1.32	1.90	1.49	1.04	1.54
V. Formic Acid 0.5%	Weight 40.1	51.3	63.1	73.1	88.2	98.8	107.1	
	Ingestion	51.6	64.8	65.4	74.5	70.3	66.0	392.6
	Protein Efficiency	1.83	1.54	1.29	1.71	1.27	1.56	1.44
VI. Formic Acid 1%	Weight 40.1	51.1	63.8	75.9	88.8	100.0	108.3	
	Ingestion	51.6	65.5	71.4	74.4	69.0	64.1	396.0
	Protein Efficiency	1.82	1.64	1.43	1.46	1.37	1.09	1.45

The second experiment was performed with adult white rats, 179-183 grams body weight, given formic acid in the drinking water at concentrations of 0.5% or 1.0% during fasting and subsequent restoration period of seven days. The effect on weight of vital organs, liver nitrogen and lipid, ascorbic acid content of the suprarenal glands, hemoglobin, and blood catalase coefficient were determined. The results are presented in Tables 10 and 11.

The authors concluded that liver nitrogen values and suprarenal gland weights were significantly lower in animals receiving 0.5% formic acid in comparison with the controls.

In the third experiment, the effect of prolonged administration of formic acid in the drinking water (1.0%) on reproduction, hematology, liver nitrogen, and ascorbic acid content of the suprarenal glands was studied. Sixty adult white rats (10 males and 50 females) were divided into five groups as follows:

Group I - Untreated controls
Group II - Females. Formic acid throughout
Group III - Males. Formic acid throughout
Group IV - Males and females. Formic acid throughout
Group V - Females. Formic acid during lactation period only.

Values for the various parameters studied were determined one month, three months, and seven months after placing the animals on the compound. The data are given in Table 12.

The authors state that the most significant finding in this study was the adverse effect of formic acid on survival of offspring during the first seven days of life. Also, hyperchromic anemia, a leucocytosis, a basophile neutropenia, and a slight lymphocytosis, were found in the formic acid groups.

3. Sollmann (430) gave rats, 200-300 gm. body weight, three to six per group, (strain, age, sex, not specified), in the drinking water, formic acid at levels of 8.2, 10.25, 90, 160, and 360 mg/kg BW/day for a period of two to 27 weeks. The animals were fed a standard diet but the treated water was the only source of fluid. Food consumption, fluid intake, and growth rates were determined. The animals were observed also for toxic symptoms throughout the experimental period. The results are presented in Tables 13, 14, and 15.

Table 10. Influence of Formic Acid on Weight of Liver, Kidney, Suprarenal Gland, and Spleen (435)

Mean data per Group

Group	Liver	Kidney	Suprarenal	Spleen
I. Casein control, 18.2%	5.443	1.302	0.2494	0.424
II. Formic Acid, 0.5%	5.143	1.191	0.2394	0.355
III. Formic Acid, 1%	5.090	1.241	0.2745	0.443
IV. Casein Control, 11.8%	4.318	1.030	0.247	0.310
V. Formic Acid, 0.5%	3.995	1.015	0.226	0.261
VI. Formic Acid, 1%	4.092	1.025	0.226	0.341

Table 11. Influence of Formic Acid on Nitrogen and Lipid Content of the Liver, on Ascorbic Acid Content of Suprarenal Glands, and on the Catalasic Coefficient (435)

Mean Data Per Group

Group	mg Liver N % Body Wt.	Liver Lipids	Ascorbic Acid Suprarenal Glands % Body Wt.	Catalasic Coefficient
I. Casein control, 18.2%	131.0	0.296	118.8	16.7
II. Formic Acid, 0.5%	128.0	0.228	125.5	19.5
III. Formic Acid, 1%	118.0	0.226	117.5	18.8
IV. Casein Control, 11.8%	115.0	0.214	126.3	17.4
V. Formic Acid, 0.5%	117.0	0.214	135.0	17.5
VI. Formic Acid, 1%	117.0	0.204	132.8	18.8

Table 12. The Influence of Prolonged Administration of Formic Acid on the Reproduction of White Rats. Mean Data Per Group. (435)

Group	Pregnant Females	Offspring Born	Offspring Born Alive	Offspring Alive at 7 days	Offspring Alive at 21 days
		Repetition I			
I	6	6.6	6.3	5.0	5.0
II	6	5.5	5.0	0.5	0.5
III	8	6.3	6.1	3.8	3.8
IV	5	6.0	5.4	2.2	2.2
V	6	7.3	7.0	5.5	5.5
		Repetition II			
I	6	6.0	4.0	4.0	4.0
II	6	4.1	2.8	2.1	2.1
III	6	6.3	6.0	6.0	6.0
IV	3	4.0	1.0	0.0	0.0
V	7	6.3	5.7	4.7	4.7

No fatalities occurred at the highest level of the acid given (360 mg/kg BW/day) and the author concluded that the occasional deaths at lower concentrations were coincidences. Untreated controls were not included in the experiment.

Food consumption and growth were markedly reduced by formic acid at a level of 360 mg/kg/BW/day for nine weeks after 17 weeks at 90 mg/kg BW/day. Fluid consumption, however, was not depressed. The lower levels of treatment had no adverse effect.

Table 13. Dosage of Formic Acid (430)

CONCENTRATION OF ACID	EXPERIMENT NUMBER	NUMBER OF ANIMALS IN EXPERIMENT	DURATION	MEAN DOSAGE, MILLIGRAMS OF ACID PER KILOGRAM OF RAT PER DAY	
Formic acid					
0.01	57	6	11	8.2	(5.6-12.1)
0.01	108	3	14	10.25	(8.4-14.3)
0.1	64	6	15	90.0	(80.0-131.0)
0.25 (after 12 weeks of 0.01)	5796	4	15	160.0	(120.0-210.0)
0.5 (after 17 weeks of 0.1)	6406	3	9	360.0	(290.0-670.0)

Table 14. Effects of Formic Acid on Growth (430)

DRUG AND CONCENTRATION	DOSAGE, CUBIC CENTIMETERS PER KILOGRAM OF RAT PER DAY	EXPERIMENT NUMBER	DURATION	OBSERVED WEIGHT	NORMAL WEIGHT	DIFFERENCE IN GRAMS	DIFFERENCE IN PER CENT OF NORMAL WEIGHT	DIFFERENCE PER CENT PER WEEK
Formic acid, 0.01 per cent	8.2	57	10	199	190	+9	+4.6	−0.46
			11	162	192	−30	−15.0	−1.3
Formic acid, 0.01 per cent	10.25	108	14	160	177	−17	−9.0	−0.63
Formic acid, 0.1 per cent	90.0	64	15	275	282	−7	−2.0	−0.13
Formic acid, 0.25 per cent (after 12 weeks of 0.01 per cent)	160.0	5796	2	165	168	−3	−1.8	−0.9
			4	222	175	+47	+26.0	+6.4
			10	235	191	+44	+23.0	+2.3
			15	216	197	+19	+9.0	+0.6
Formic acid, 0.5 per cent (after 17 weeks of 0.1 per cent)	360.0	6406	9	180	295	−115	−56.0	−6.7

Table 15. Mortality (430)

DRUG AND CONCENTRATION	DOSAGE	EXPERIMENT NUMBER	NUMBER OF ANIMALS	WEEKS OF FATALITIES	TOTAL DURATION	PER CENT OF FATALITIES
Formic acid, 0.01 per cent	8.2	57	6	11	11	16
Formic acid, 0.01 per cent	10.25	108	3	0	14	0
Formic acid, 0.1 per cent	90.0	64	6	0	15	0
Formic acid, 0.25 per cent (after 12 weeks of 0.01 per cent)	160.0	5796	4	2	15	25
Formic acid, 0.5 per cent (after 17 weeks of 0.1 per cent)	360.0	6406	3	0	9	0

C. Guinea Pigs

Amdur (007) exposed guinea pigs, seven to 16 per group, (strain, age, sex, and weight not given), to air containing formic acid at levels ranging from 0.34 to 42.5 ppm, alone and with sodium chloride aerosol, for a period of one hour. Intrapleural pressure, tidal volume, and the rate of flow of gas in and out of the respiratory system were determined at five-minute intervals to assess the effect of the irritant. Normal values were obtained during a pre-treatment control period of one-half hour. Each animal, therefore, served as its own control. Also studied were responses to the irritant administered through a tracheal canula to by-pass the protective effect of the upper airway. Post-exposure periods varied from one to three hours. The results are presented in Tables 16 and 17, and Figs. 4, 5 and 6.

Formic acid at concentrations as low as 0.3 ppm for one hour caused an increase in resistance (pulmonary flow) and a decrease in compliance (elastic recoil) which were statistically significant. Concentrations of 1-3 ppm produced an increase in respiratory work, and above 10 ppm, respiration rate and minute volume decreased significantly. The effect of formic acid was not potentiated by the sodium chloride aerosol. In this study formic acid proved to be a more potent respiratory irritant than formaldehyde.

D. Rabbits

1. Smyth et al.(429) subjected male New Zealand giant albino rabbits, 2.5-3.5 kg BW, four per group, to graded doses of ethyl formate applied to the skin (hair removed by clipping) over about 1/10 of the body surface and retained in contact with the skin by means of an impervious plastic film. After an exposure period of 24 hours, the film was removed and the animals observed for a period of 14 days for signs of systemic toxic effects. All rabbits survived the maximum dosage, 20 mg/kg BW, that could be retained in contact with the skin by the method employed. No adverse effects were reported.

The same authors (429) also applied varying amounts and dilutions of ethyl formate to the clipped skin and to the eyes of albino rabbits, five per group (strain, age, weight, and sex not given), and determined the degree of primary skin irritation or eye injury over a period of 24 hours. The results were scored on the basis of a "10-grade ordinal series" in which Grade 1 indicated the mildest effect and Grade 10 the most severe reaction. Ethyl formate produced a so-called severe corneal burn (Grade 4) from a relatively small amount introduced into the eye; dermally, it was quite non-toxic (Grade 1).

Table 16. Response of Guinea Pigs to One-Hour Exposure to Formic Acid (007)

HCOOH–P.P.M.		0·34 ± 0·02	1·0 ± 0·08	2·8 ± 0·15	6·6 ± 0·5	13·5 ± 0·9	42·5 ± 3·8
Number of Animals		7	8	8	16	8	7
Resistance	Control	0·78	0·71	0·77	0·77	0·81	0·86
cm H_2O/ml/sec	Exposure	1·01[b]	1·02[b]	1·28[b]	1·40[a]	1·56[a]	2·08[a]
Δ-Exposure-Control		+0·23	+0·31	+0·51	+0·63	+0·75	+1·22
SE-Standard Error of Difference		0·053	0·059	0·165	0·049	0·100	0·157
Compliance	Control	0·26	0·23	0·24	0·25	0·21	0·20
ml/cm H_2O	Exposure	0·21[d]	0·18[b]	0·19[c]	0·19[a]	0·14[b]	0·13[b]
Tidal Volume	Control	1·85	1·91	1·88	1·84	1·70	1·70
ml	Exposure	1·83	1·71	2·12	1·82	1·82	1·92
Frequency	Control	95	96	101	100	107	100
Breaths/min	Exposure	89	101	90	99	98	58[b]
Minute Volume	Control	176	183	183	184	183	170
ml/min	Exposure	165	172	175	179	173	110[b]
Elastic Work	Control	624	762	744	677	736	722
g-cm/min	Exposure	710	820	1065[c]	974[c]	1160[c]	822
Resistive Work	Control	990	980	1140	1070	1100	1020
g-cm/min	Exposure	1100	1250	1917[b]	1860	2040[b]	1060
Total Work	Control	1614	1742	1884	1747	1836	1742
g-cm/min	Exposure	1810	2070	2982[b]	2834[c]	3200[b]	1882

Different from control at P: a = ·001, b = ·01, c = ·02, d = ·05

Table 17. Resistance Values One Hour After End of Exposure (007)

		HCHO						
HCHO P.P.M.		0·05	0·31	0·58	1·22	3·5	11·0	49
Number of Animals		18	13	23	4	10	10	8
Resistance	control	0·71	0·64	0·64	0·80	0·68	0·62	0·65
cm H_2O/ml/sec	1 hr. post exposure	0·82	0·62	0·71	0·93	0·82	0·75	1·03
$\bar{x}$-Post Exposure—control		+0·11	−0·02	+0·07	+0·13	+0·14	+0·13	+0·37
$S\bar{x}$-Standard Error of Difference		0·05	0·056	0·038	0·125	0·080	0·071	0·065
Level of Significance $P<$		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	0·01
		HCHO—Tracheal Cannula						
HCHO-P.P.M.		0·90	5·2	20	50		1·14	3·6
NaCl-mg/m³		—	—	—	—		10	10
Number of Animals		7	7	10	6		8	6
Resistance	control	0·40	0·31	0·44	·048		0·38	0·44
cm H_2O/ml/sec	1 hr. post exposure	0·46	0·41	0·87	1·04		0·98	1·24
$\bar{x}$-Post Exposure—control		+0·06	+0·10	+0·34	+0·56		+0·60	+0·80
$S\bar{x}$-Standard Error of Difference		0·036	0·049	0·213	0·198		0·207	0·196
Level of Significance $P<$		N.S.	N.S.	N.S.	0·05		0·05	0·01
		HCOOH						
HCOOH-P.P.M.		0·34	1·0	2·8	6·6	13·5	42·5	
Number of Animals		7	8	8	16	8	7	
Resistance	control	0·78	0·71	0·77	0·77	0·81	0·86	
cm H_2O/ml/sec	1 hr. post exposure	0·75	0·94	1·02	1·05	0·98	1·54	
$\bar{x}$-Post Exposure—control		−0·03	+0·23	+0·25	+0·38	+0·17	+0·68	
$S\bar{x}$-Standard Error of Difference		0·090	0·154	0·146	0·077	0·096	0·222	
Level of Significance $P<$		N.S.	N.S.	N.S.	0·01	N.S.	0·02	

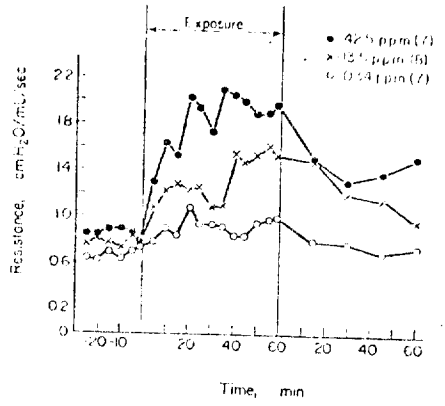

Figure 4. Time Course of the Resistance Change Produced by Formic Acid (007)

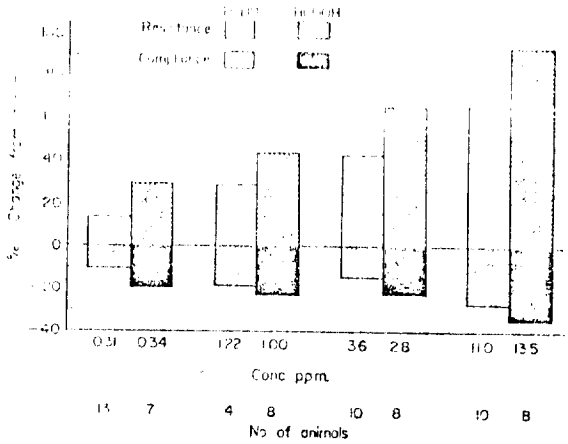

Figure 5. Comparison of Changes in Resistance and Compliance Produced by Equal Concentrations of Formaldehyde and Formic Acid (007)

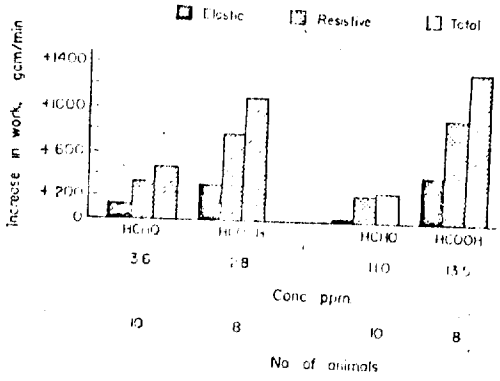

Figure 6. Comparison of the Changes in Respiratory Work Produced by Equal Concentrations of Formaldehyde and Formic Acid (007)

2. Lund (272) in a study on the metabolism and excretion of methanol and formic acid, injected two full-grown male rabbits, weighing 3150 and 3300 grams, subcutaneously with a single dose of sodium formate, consisting of 317 and 303 mg/kg BW, respectively. Although the experimental period lasted only 48 hours, apparently neither animal manifested any toxic symptoms.

3. Sollmann (430) reported that an early study by Lebbin (1916) revealed that continuous administration of either acetic acid or formic acid (dosage, route, and duration not given) caused kidney damage.

4. Gross (260) noted that rabbits, like guinea pigs, suffered marked depression of the central nervous system when placed in an atmosphere containing ethyl formate at concentrations of 40 to 130 mg per liter, and that pneumonia frequently developed. Subcutaneously, however, doses as large as 1000 mg/kg BW were tolerated without local or systemic symptoms.

5. von Oettingen (491), in a review of early studies on the effect of ethyl formate administered intravenously to the rabbit, noted that intrajugular injection of 28 mg/kg BW of the undiluted ester caused an increase of the respiratory volume without depressing the CNS, whereas, in another study, doses as high as 250 mg/kg BW intravenously (anatomic site not given) in the form of a 5% solution, were tolerated without evidence of any effect.

E. Dogs

Lund (271) in a study of the metabolism and excretion of methanol and formic acid, injected a full-grown male dog, 10.1 kg BW, (strain, sex, and age not given) subcutaneously with a single dose of sodium formate, consisting of approximately 200 mg/kg BW (40 ml of a 5% solution). The animal manifested no toxic signs over an experimental period of 27 hours.

In a second experiment by the same author, a single dose of approximately 100 mg/kg BW (50 ml of a 2% solution), injected into the washed, empty bladder through a catheter tube, was tolerated without toxic symptoms.

F. Sheep

Neumark et al.(315) gave (stomach tube or rumen canula) two clun forest wethers (age and weight not specified), single doses of formic acid, approximately 150 mg/kg BW. This was done in an effort to determine if the appetite depressant effect of this compound in sheep was due to systemic action or to

a local effect on one or more areas of the stomach. (Previous studies showed that the quantity of silage eaten by sheep was reduced when fermentation products, such as formic acid, formaldehyde, and histamine were present). In another experiment, the acid was injected intravenously. Also, in one test, sodium formate was used in place of formic acid. The effects of histamine, and of histamine in combination with formic acid, were determined in other experiments. Control data (no treatment) were obtained on all of the sheep in preliminary experiments. During the experimental period, the animals were maintained on a ration consisting of 350 grams of chopped hay with 100 grams of flaked maize fed twice daily. The effect on eating time of offered food was determined. The results are presented in Tables 18, 19, 20 and 21.

The data obtained showed that the area between the cardia and fundic portions of the abomasum is sensitive to formic acid. When the compound was introduced into this area at a level of 150 mg/kg BW, there was a marked adverse effect on the eating time of one of the two animals used (sheep 174). A combination of formic acid and histamine had a much stronger depressant effect (see Table 18). Experiments with dyes revealed that substances introduced into the above-mentioned area of the stomach passed rapidly into the abomasum. Formic acid alone, or in combination with histamine, introduced into the rumen via a canula, had no effect on the time sheep took to eat offered food. It is known that formic acid is rapidly destroyed in the rumen and provides a source of hydrogen for methane formation. Administration of formate intravenously had no effect on the eating behavior.

The authors suggest that the depressing effect of formic acid on appetite is caused by its local irritant action on the nerve endings of the stomach as it rapidly penetrates the epithelial layer. Sodium formate does not cause this effect.

G. Cattle

1. Castle (074) fed 12 Ayrshire cows, (age and weight not given), grass silage containing formic acid at a level of 1/2 gallon per ton of herbage, for a period of twelve weeks. Control groups on silage without additive (wilted and unwilted) were included. The silages were fed to the cows ad libitum with a supplement of moist barley and groundnut cake. Food intake, weight gain, milk yield, and solids-not-fat content of the milk were determined.

No toxic effects were noted at any time during the study. The formic acid-treated silage proved to be superior to the control diet with respect to all parameters.

Table 18. The Effects of Introducing Formic Acid, Histamine, Saline and Other Agents into the Rumen via a Stomach Tube on the "eating time" of Sheep (315)

No. of trials	Solution introduced	Effect on 'eating time'
5	1 l. saline	None
4	1 l. 0·2 M formic acid	Marked effect in 3 trials. Slight effect in 1 trial
4	1 l. 0·2 M formic acid + 360–541 mg histamine (3 trials) or 902 mg histamine (1 trial)	None at lower rate of dosage. Marked at high rate
	Uncontrolled length of tube used	
7	1 l. 0·2 M formic acid + 497–660 mg histamine (tube introduced to 72–73 cm)	Marked effect in all trials
1	1 l. 0·2 M formic acid plus 497 mg. histamine (tube introduced to 87 cm)	None
1	1 l. 0·2 M acetic acid (tube introduced to 72 cm)	None
1	1 l. 0·25 M acetic acid plus 497 mg. histamine (tube introduced to 72 cm)	Marked effect
2	1 l. 0·2 M sodium formate (tube introduced to 72 cm)	None

Table 19. The Responses of Sheep to Infusions of Formic Acid, Histamine or Both into the Abomasum (315)

Sheep	Treatment	Response
	(Infused into pyloric region)	
174	0·016 M formic acid plus 42 mg histamine	None
174	0·026 M formic acid + 75 mg histamine	Rapid respiration. Finished food in 31 min.
174	94·5 mg histamine	Rapid respiration. Finished food in 35 min.
174	0·08 M formic acid	None
174	0·19 M formic acid	None
	(Infused into fundic region)	
265	0·15 M formic acid plus 120·6 mg histamine	Normal respiration. Stopped feeding after 6 min. 150 g left after 42 min. Feeding normally after 24
70		Normal respiration. Stopped eating after 9 min. and did not feed normally for 2 days
31		Normal respirations. Did not feed after infusion and food consumption depressed for several days

Table 20. The Response of Food Intake to Infusion of Formic Acid and/or Histamine into the Jugular Vein (315)

No. of trial	Treatment*	Response
1	0·0005 M formic acid plus 1 mg histamine	Finished eating after 27 min; several very slight interruptions during eating
2	0·001 M formic acid	No
3	0·001 M formic acid 1 mg histamine	No
4	0·002 M formic acid 2 mg histamine	Respiration rate raised, eating speed lowered (31 min
5	0·001 M formic acid 1 mg histamine	No
6	0·004 M formic acid	No (finished eating after 24 min.)
7	3·2 mg histamine	Respiration rate raised, finished eating after 32 min.

* Formic acid and/or histamine were dissolved in 10 c.c. and in 8 c.c. saline in trials 1–6 and 7 respectively.

Table 21. The Concentration of Acetic and Formic Acids in the Jugular Blood of Sheep no. 174 Before and After Treatment* (315)

		Infusion by stomach tube		Infusion by rumen fistula	
No. of trial	Time of blood collection	Formic acid (μg/ml blood)	Acetic acid (μg/ml blood)	Formic acid (μg/ml blood)	Acetic acid (μg/ml blood)
1	Before treatment	14·0	43·7	5·9	29·0
2	6 min after treatment	—	—	16·9	27·0
3	30 min after treatment	76·4	68·7	8·9	28·7

* One litre 0·2 M formic acid solution, containing 861 mg histamine, was infused by stomach tube into the rumen of sheep no. 174, and 5 days later an equal solution, containing only 581 mg histamine, was introduced into the rumen of the sheep by rumen fistula.

2. Waldo et al (496) fed Holstein heifers, paired on body weight (89-337 kg), Williamsburg alfalfa and Potomac orchard grass silage, treated at the field chopper with an additive of 0.49, 0.52, or 0.48 (w/w) of 90% formic acid solution. The silages were stored for 28, 29, and 128 days, respectively, before feeding (experiments 1, 2, 4). Each silage was fed to the heifers ad libitum as the sole ration. Control silages were included in each experiment. The organic acid concentration is shown in Table 22. Food intake, digestibility, and growth rates were determined. The results are presented in Tables 23 - 26. Another experiment (Experiment 3) was conducted in which the silage was treated with a combination of formic and acetic acids.

No toxic effects were reported. Weight gains of the animals on the formic acid silage were better for the most part than those of animals on the control ration.

3. Bovine erythrocytes are hemolyzed by ethyl formate in vitro. The minimal lytic concentration found was 5.25 grams (0.71 mole) per liter (491).

Table 22. Organic Acid Concentration in Silages. (496)

	Experiment 1		Experiment 2		Experiment 3		Experiment 4		Overall means		
riteria	Formic	Untreated	Formic	Untreated	Formic	Untreated	Formic	Untreated	Formic	Untreated	SE of mean[a]
samples	4	4	4	4	4	4	5	5	..	..	..
acetic (% DM)	5.29	7.42	2.96	4.14	1.06	1.62	5.57	0.31	3.72	3.35	1.21g
tic (% DM)	4.94	4.13	3.79	1.52	.70	.73	1.22	2.57	2.66	2.24	.55g
propionic (% DM)	.08	.02	.16	.07	.01	.07	.06	.76	.08	.23	.14g
valeric (% DM)	.06	0	.17	.06	0	.04	.13	1.85	.08	.59	.33g
mic (% DM)	.56	.10	.28	.18	.79	.06	.99	.15	.66	.13	.12e
cal (% DM)	10.96	11.67	7.35	5.96	2.56	2.54	7.97	5.56	7.21	6.16	.19g

[a] Standard error of a mean and statistical significance is for overall means: e, $P<.05$ and g, $P>.10$.

Table 23. Least Squares Treatment within Experiment Means and Standard Errors of Ad Libitum Forage Intake and Heifer Growth (496)

Criteria	Experiment 1		Experiment 2		Experiment 3		Experiment 4		SE of a mean[b]
	Formic	Untreated	Formic	Untreated	Formic	Untreated	Formic	Untreated	
Days	72	72	69	69	84	84	36	36	..
No. animals	15	15	14	14	10	10	10	10	..
Daily gain (g)	763	653	570	651	951	824	949	64	49.0a
Daily gain (g/kg$^{.75}$)	12.7	10.8	9.6	11.0	13.5	11.7	12.4	.9	.74a
Daily DM consumed (% BW)	2.53	2.66	2.35	2.54	2.57	2.64	1.80	1.46	.054a
Daily Meal DE consumed	18.5	18.9	16.2	16.9	18.6	19.6	16.0	12.0	.41a
Daily kcal DE/kg$^{.75}$	300	311	276	286	263	276	209	160	5.7a
Daily Meal DE for growth	9.7	10.2	7.7	8.3	8.3	9.3	4.9	1.1	.35a
Meal DE for growth/kg gain	12.5	15.5	14.8	13.4	8.7	11.6	5.4	6.6	.4g
Gain/metric ton DM stored (kg)	98	100	84	96	122	82	146	11	.

[b] Standard error of a mean is for n = 10. Statistical significance is for experiment by treatment interaction: a, P<.001 and g, P>.10.

Table 24. Least Squares Treatment Means and Standard Errors of Ad Libitum Forage Intake and Heifer Growth (496)

Criteria	Formic	Untreated	SE of a mean[b]
No. animals	49	49	..
Daily gain (g)	808	548	142.4g
Daily gain (g/kg$^{.75}$)	12.1	8.6	1.88g
Daily DM consumed (% BW)	2.32	2.33	.076g
Daily Meal DE consumed	17.3	16.8	.77g
Daily kcal DE/kg$^{.75}$	262	255	10.3g
Daily Meal for growth	7.6	7.2	.71g
Meal DE for growth/kg gain	10.4	11.8	.70g
Gain/metric ton DM stored (kg)	113	72	23.7g

[b] Statistical significance: g, P>.10.

Table 25. Least Squares Treatment Within Experiment Means and Standard Errors for Digestibility and Nitrogen Utilization (496)

	n	Dry matter	Energy	Cellulose	Hemicellulose	Lignin	Nitrogen digested	Nitrogen retained	Fecal solubles
Experiment 1		(%)						(g/day)	(g/100 g feed DM)
Formic ad lib	4	62.2	63.9	61.8	50.1	5.5	71.3	41.7	16.1
Formic maintenance	4	64.2	65.6	66.5	50.8	8.8	72.1	10.6	14.9
Untreated ad lib	4	64.5	65.9	65.8	35.6	14.9	72.6	46.2	15.8
Untreated maintenance	4	65.8	67.5	66.9	41.8	11.7	75.2	12.0	14.8
Experiment 2									
Formic ad lib	4	62.5	62.5	70.5	61.9	16.6	70.4	33.0	16.2
Formic maintenance	4	63.8	63.4	70.8	66.2	12.8	71.4	9.7	15.1
Untreated ad lib	4	63.2	62.7	69.1	60.8	17.1	66.8	20.9	17.0
Untreated maintenance	4	65.2	64.4	71.0	67.0	18.7	68.5	21.8	16.1
Experiment 3									
Formic ad lib	4	56.0	55.0	60.6	62.4	6.5	58.4	26.1	21.6
Formic maintenance	4	57.0	55.7	60.2	57.6	3.9	61.4	− 2.8	19.4
Untreated ad lib	4	58.2	56.4	65.6	44.6	16.6	57.4	29.8	20.0
Untreated maintenance	4	58.4	57.6	66.4	51.4	16.6	59.4	6.5	20.4
Experiment 4									
Formic ad lib	4	56.6	57.0	67.2	73.6	16.0	61.9	36.8	20.8
Formic maintenance	4	56.8	57.5	67.3	74.0	14.2	63.0	14.8	20.4
Untreated ad lib	4	46.6	50.7	58.2	62.8	− 9.7	51.8	−16.6	24.4
Untreated maintenance	4	48.3	51.3	59.5	67.1	−10.5	53.8	−17.0	23.6
SE of a mean[h]		1.31b	1.47e	1.74b	3.26g	5.78d	1.70d	7.08b	.50b

[h] Statistical significance is for experiment by treatment interaction: b, P<.005; d, P<.025 and g, P>.10.

Table 26. Least Squares Treatment Means and Standard Error for Digestibility and Nitrogen Utilization (496)

Criteria	Formic	Un-treated	SE of a mean[a]
n	32	32	
Dry matter (%)	59.9	58.8	1.12g
Energy (%)	60.1	59.6	.79g
Cellulose (%)	66.0	65.3	1.19g
Hemicellulose (%)	62.1	53.9	1.27b
Lignin (%)	10.5	9.4	3.40g
Nitrogen (% digested)	66.2	63.2	1.02f
Nitrogen (g retained/day)	21.2	12.9	5.36g
Fecal solubles (g/100 g feed DM)	18.1	19.0	.38g

[a] Statistical significance: b, $P < .005$; f. $P < .10$ and g, $P > .10$

H. Human toxicity

Sollmann (430) and von Oettingen (491) have reviewed the early studies on the effect of formic acid and formates on human volunteers. In one study 500 mg. amounts of formic acid in lemonade given daily for four weeks caused no harmful effects. Larger doses (amount not specified) caused local reactions analogous to those produced by acetic acid.

Ingestion of 3-4 grams of sodium formate (50-70 mg/kg BW) caused albuminuria and hematuria in one of three human subjects but the condition cleared up after five days (491). In another study, daily doses of 150 mg/kg BW per os for some time (duration not given) caused no harm (430). Intravenously, a single dose of four grams (20 ml of a 20% soln.) of sodium formate was tolerated without evidence of toxicity (491). On the other hand, Stern (445) found that large doses, 2-3 grams given several times daily, may cause vertigo, nausea, vomiting, albuminuria, hematuria, tenesmus, dyspnea, and lowered body temperature.

Formic acid and formates are quite toxic for man via the respiratory tract. Exposure to the vapors or dust may cause pallor, hyperemia of the conjunctivae and sclera, and gastrointestinal distress. Inhalation in concentrations as low as 32 mg per liter of air causes progressive irritation of the eye and mucous membranes which may last four hours after withdrawal of the

irritant (491). The maximum acceptable concentration of ethyl formate, according to the American Conference of Governmental Industrial Hygienists, in air is 100 ppm for 8-hour exposures daily (009).

Gray (162) studied the effect of a series of organic acids on human tooth enamel by subjecting sections of teeth to varying concentrations of the acids over a pH range of 3.0 to 6.0 and determined the degree of caries-like lesion formation. The results revealed that formic acid at pH 4.5 had a pronounced effect on tooth enamel. At pH 4.0, the effect was considerably greater (see Figs. 7 and 8).

Formic acid is very corrosive to the skin and mucous membranes, and precautions should be taken to avoid direct contact with the chemical or breathing formate dusts and mists (438). Even though skin contact may be slight and only moderately painful at first, the after-effects can be severe. Following the initial reaction of hyperemia and erythemia, the skin may show "a cooked appearance, and after 24 hours, parchment-like necroses which are slow to heal". Orally, formic acid and formates cause irritation of the gastrointestinal tract followed by vomiting and diarrhea (491).

A number of conflicting reports have appeared concerning possible roles of formic acid and formaldehyde, which are intermediate oxidation metabolites, in methyl alcohol poisoning in man. Lund (270) reported on concentrations of methanol and formic acid in the blood and urine of human victims poisoned with methyl alcohol. The results are presented in Tables 27 and 28.

Table 27. Formic Acid Excretion of Human Subjects Poisoned with Methanol. (270)

A: Man, aged 31, weight 62 kg, consumed 25 ml (20 g) methanol (Pobl 1893).
B: Woman, aged 25, consumed about 80 g methanol (Harrop and Benedict 1920)

Days after intake	excreted formic acid in urine: mg in 100 ml A	B	mg total A	B
1	2.3	--	37.4	--
2	32.5	126	420	--
3	6.1	--	89.6	--
4	2.4	60	29.2	--
11	--	7	--	--

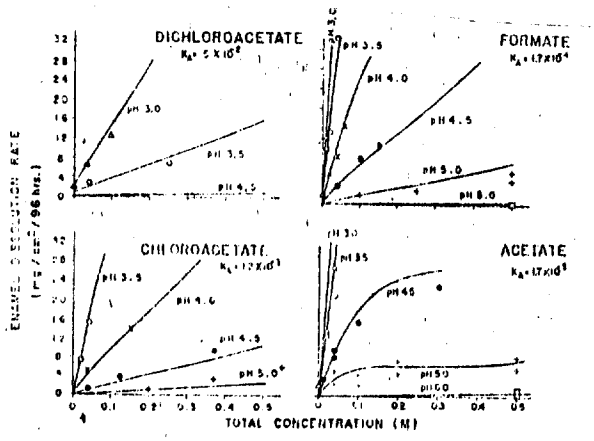

Figure 7. The enamel dissolution rate during caries-like formation in 6% hydroxyethylcellulose + acid solutions is shown for four acids with decreasing dissociation constants. The solid lines are calculated values from a single equation fitted to the results. (162)

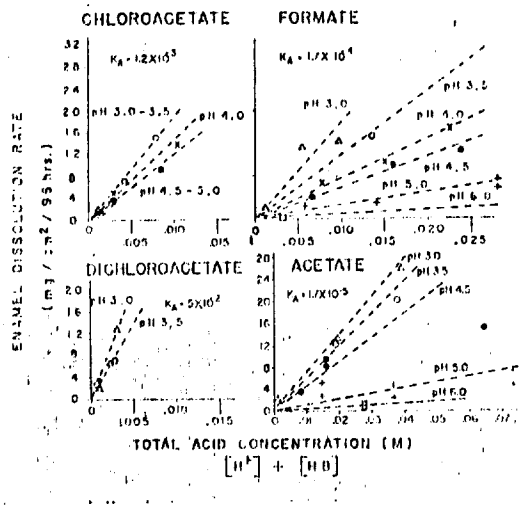

Figure 8. The enamel dissolution rate as a function of pH and total available acid is shown for the 4 different acids of Fig. 7. The rate is pH dependent and linear with respect to total acid concentration except for acetate at high pH levels. (162)

Table 28. The Concentration of Methanol and Formic Acid in Blood, Liver and Urine from Human Beings Dying of Methanol Poisoning (270).

Case No.	mg methanol in 100 g of blood	liver	urine	mg formic acid in 100 g of blood	liver	urine
10. V.H.	74	106	140	68.1	59.6	785
11 O.R.*		--	240	--	98.6	475

Watts (504) studied the effect of formic acid, formaldehyde, and methanol on the oxidation of glucose, succinate, and ascorbate by rat liver slices and homogenates, in order to shed some light on the mechanism of methanol poisoning (see this section, A.). Although formic acid, in concentrations approximating those found in fatal methanol poisoning in the rabbit, depressed respiration by 50%, formaldehyde was found to be ten times more potent in this respect. On the basis of a comprehensive review of the literature, plus his own experimental findings, Sammartino (403) concluded that methanol per se played the main role in methyl alcohol poisoning in man. The known physiologic effects of these compounds, modes of action, and pattern of toxic effects in methanol poisoning led him to this view.

III. Long-term Studies

A. Rats

Malorny (275) recently concluded three long-term oral toxicity studies on the rat with calcium formate and sodium formate administered in the drinking water.

The first experiment was started with Wistar rats; eight males and twenty-four females, 160-210 grams body weight. These animals were given calcium formate in the drinking water at a level of 0.2% throughout their life span. Fluid intake measurements indicated a dosage of 150-200 mg/kg BW daily. A control group of eight animals of the same specifications was included. The experiment was continued with the progeny of the original animals. After more than three years and five generations, no deaths or toxic symptoms attributable to the compound were noted. Fertility, pregnancy, and development of fetuses and offspring also were normal. The data are presented in Tables 29 and 30.

Table 29. Effect on Rats of Calcium Formate (0.2%) Administered[a] Orally in the Drinking Water (275)

Weeks	0.2% $Ca(HCOO)_2$ in the drinking water I♀	II♀	III♀	IV♂	Controls V♀	VI♂
1	175	170	170	195	170	200
	±8.9	±12.5	±11.0	±9.4	±11.2	±9.8
2	205	190	185	230	195	235
3	220	190	195	250	210	260
4	230	200	200	270	225	275
5	240	205	210	285	235	288
6	240	215	220	300	238	290
7	240	220	225	310	240	305
8	255	220	230	320	260	318
10	262	228	235	340	268	340
12	275	240	238	353	270	360
	±10.6	±9.8	±9.5	±13.4	±9.0	±14.2
15	283	245	240	355	290	370
	±9.5	±10.5	±13.0	±11.8	±10.6	±12.7

[a]Four rats per group. Body weights - Mean values and Standard Deviations

Table 30. Effect on Rats of Generations I-III of Calcium Formate (0.2%) Administered[a] Orally in the the Drinking Water (275)

	I. Generation		II. Generation		III. Generation	Control
	n=11	n=10	n=9	n=8	n=10	n=10
Weight at birth	5.0 ±.46	5.8 ±.61	5.5 ±.33	4.9 ±.55	5.6 ±.58	5.2 ±.52
1 week	16.0	19.5	18.2	15.9	14.8	14.5
2 week	34.0	32.5	31.7	28.0	29.1	33.0
3 week	49.0	55.0	48.0	48.0	52.0	53.0
4 week	79.0	84.0	78.0	85.0	76.0	83.0
	±3.8	±3.7	±4.0	±3.2	±3.6[1])	± 4.2
5 week	108	118	112	109		113
6 week	128	138	136	134		145
7 week	160	159	155	152		165
8 week	179	174	177	180		182
	±3.9	±4.8	±6.0	±4.3		±5.1
10 week	216	220	217	224		221
14 week	291	297	301	295		293
18 week	297	309	-	-		-
20 week	309	318	310	313		320
	±5.0	±6.2	±6.8	±5.2		±5.8

[1]The test is not pursued further.

[a]Mean B ody Weights with Standard Deviation

The second experiment with calcium formate by Malorny (275) was similar in all respects to the first except that the formate concentration was doubled (0.4%) in the drinking water, and the data reported were for two generations of animals over a period of two years. Again, no deaths or toxic effects resulted from the calcium formate administered. Moreover, gross and pathologic examination of more than 250 rats from three generations employed in these experiments, revealed no evidence of chronic poisoning or malignancy.

The third experiment in this series conducted by Malorny (275) was started with the same number of Wistar rats (375 grams mean body weight) as used in the preceding experiments. Sodium formate, however, was used in place of calcium formate, and the concentration in the drinking water was increased to 1%. The daily intake was found to be 274 mg per animal (730 mg/kg BW, approx.). Physiologic studies revealed that 13.8% of the compound ingested, calculated as formic acid, was excreted in the urine daily. No fatalities or toxic effects attributable to the compound over the experimental period of 1-1/2 years were reported.

IV. Special Studies

A. Bacteria

1. Demerec (097) investigated formic acid and a number of other compounds for mutagenic potentiality on the basis of their ability to induce back-mutation from streptomycin-dependence to non-dependence in Escherichia coli (strain Sd-4). Varying concentrations of formic acid in distilled water (See Table 31) were inoculated with streptomycin-dependent E. coli (Sd-4), and incubated at 37°C for six hours. Untreated control cultures were prepared in an analogous manner by inoculating an equal volume of distilled water with the test organism. At the end of the exposure period, both treated and control cultures were plated on streptomycin agar to calculate the percentage of survivors, and on streptomycin-free agar to determine the number of mutants. The results are presented in Tables 31 and 32.

Formic acid was one of 19 compounds found to be mutagenic in this study (Table 32). The data indicate it to be moderately mutagenic, in comparison with the others, with respect to its ability to induce back-mutation in Escherichia coli (Sd-4) from streptomycin-dependence to non-dependence.

Table 31. Results of Experiments Testing Induction of Back-mutations in Streptomycin-dependent E. coli Treated with Certain Chemicals (097)

Chemical	Concentration %	Treatment (hours)	Survival %	Treated			Control		
				No. of plates	Total no. of bacteria	Mutants per 10^8 bacteria	No. of plates	Total no. of bacteria	Mutants per 10^8 bacteria
Lactic acid (*continued*)	0.021	3	7.5	8	1.1×10^9	40.2			4.5
	0.020	3	6.8	8	1.7×10^9	17.0	5	1.6×10^9	15.3
	0.020	3	4.6	8	6.7×10^9	32.9	5	9.2×10^7	27.3
	0.020	4	2.5	8	2.9×10^7	34.7	6	8.5×10^7	9.4
	0.020	3	1.9	8	2.6×10^7	11.4	6	1.0×10^9	4.8
Sodium lactate	2.5	3	85.	8	1.5×10^9	7.3	5	1.1×10^9	12.1
	3.0	3	61.	8	1.7×10^9	16.4	5	1.6×10^9	15.3
	2.0	24	8.3	8	8.7×10^7	5.8	6	7.9×10^7	10.1
	2.5	24	1.4	8	3.8×10^7	5.2	5	1.7×10^9	9.2
Formic acid	0.0070	3	100.	8	1.5×10^9	18.1	6	1.1×10^9	2.7
	0.0060	3	93.	8	1.4×10^9	18.4			2.7
	0.0050	3	77.	8	1.3×10^9	20.2	5	1.1×10^9	12.1
	0.0065	3	30.	8	8.2×10^9	44.0	5	1.7×10^9	9.2
	0.0060	3	20.	8	5.0×10^9	48.3	5	1.6×10^9	15.3
	0.0065	3	19.	8	4.6×10^9	24.4	5	1.5×10^9	3.3
	0.0060	3	15.	8	1.4×10^9	27.7	6	7.1×10^7	2.8
	0.0075	3	3.4	8	8.2×10^7	38.0			3.3
	0.0070	3	2.8	8	2.6×10^7	38.5			2.8
Formaldehyde	0.01	3	61.	2	7.6×10^7	400.	2	1.3×10^9	26.2
	0.01	3	58.	5	6.8×10^9	133.	4	9.4×10^9	15.5
	0.02	3	58.	5	6.8×10^9	157.			15.5
	0.01	3	48.	4	3.7×10^7	245.	4	7.6×10^7	79.
	0.01	3	48.	4	3.7×10^9	470.	4	7.6×10^9	68.
	0.01	3	21.	8	1.3×10^9	120.	4	7.3×10^7	12.3
	0.02	3	16.	8	1.0×10^9	129.			12.3
	0.04	3	9.0	7	1.5×10^9	326.			15.5
	0.05	3	1.7	10	3.2×10^9	560.			79.

Table 32. Summary of the Data on Mutagenic Chemicals, Showing Highest and Lowest Frequencies of Mutants Observed in Experiments Using Different Treatments (Expressed in Percentages of Survivors) (097)

	Survivors (per cent)			Controls
	50–100	5–50	less than 5	
	No. of mutants per 10^8 bacteria			
Boric acid	27	16–82	19–57	6–31
Ammonia	5	2–10	38–121	3–13
Hydrogen peroxide	20–29	121–124	27–175	5–7
Copper sulfate	6	4–21	40–56	2–21
Acetic acid	8	15–36	57	7–10
Lactic acid	...	11–40	11–35	5–27
Formic acid	18–20	24–44	38–39	3–15
Formaldehyde	133–400	120–326	560	12–79
Phenol	3–85	...	124–820	1–75
Alpha-dinitrophenol	3–34	14–56	6–97	3–13
Trinitrophenol	15	9–132	27–68	3–14
Carbamate, ethyl	19–27	7–53	40–99	6–20
n-propyl	12–28	8–30	10–35	2–12
n-butyl	21	5–21	6–9	2–12
isoamyl	8–11	6	7	2–4
Neutral red, light	57	118–122	178	7–11
dark	11–17	...	...	7–15
Acriflavine	...	59–78	...	14
Caffeine	16	13–35	20	3–18
Necrosin	16–26	18	172	4–10

2. Freese et al (141) reported that formic acid and two other oxidation products of formaldehyde, as well as formaldehyde itself, at levels of 10^{-1} M and 10^{-2} M, did not inactivate or mutate transforming bacterial DNA in vitro at a significant rate in their study.

B. Insects

Stum-Tegethoff (450) investigated the susceptibility of Drosophila germ cells to the mutagenic effect of formic acid, formaldehyde, and some related compounds with respect to sex-linked lethals in males.

A standard strain of Drosophila melanogaster, Oregon-K (inbred for about 10 years), with a spontaneous mutation rate of 0.15% sex-linked lethals in males, was used throughout. Adult males were subjected to the compounds in the vapor phase, and larva to their effect when incorporated in a nutrient medium of agar, killed brewer's yeast, corn meal, and sucrose - pH 4.2-5.6. To test for sex-linked lethals, about 50 treated males were individually crossed with one or two virgin females of the M-5 strain (inbred for about 10 years). Three successive broods were produced by transferring the males to two fresh virgins every third day. The results are presented in Tables 33, 34, and 35.

Formic acid at a level of 0.1% (final concentration), alone and in combination with formaldehyde, proved to be mutagenic for Drosophila germ cells. All germ layers were susceptible in the vapor phase. Spermatocytes I were especially sensitive to their action per os. Volatile acid was necessary for the mutagenic activity of formaldehyde in the vapor phase and a low pH for all compounds in the feeding experiment. When the pH was raised to 7.5, for instance, the induced mutation rate was only slightly higher than the spontaneous rate. The author postulated that the mutation mechanism involved catalase inhibition which promoted the formation of peroxides or free radicals which in turn interfered with DNA replication.

C. Chick embryos

Malorny (275) injected 2 and 4-day old embryonated chicken eggs with single doses of sodium formate (5, 10, or 20 mg per egg) and then observed the embryos for toxic signs and teratogenic effects throughout the hatching period.

Table 33. Formic Acid-induced Mutations in Drosophila melanogaster, Vapor Experiments (450)

treatment substance	concentration %	brood 1st n[1]	1st % [2]	2nd n	2nd %	3rd n	3rd %	total n	total %
nF	7.0	—	—	—	—	—	—	3803	0.16
aF	7.0	436	0.69	712	1.97	423	1.18	1571	1.40
FA	0.1	1008	1.12	1130	1.42	850	1.41	3048	1.31
AA	0.1	1703	0.82	1359	0.66	1270	1.10	4332	0.85
HA	0.01	1047	0.67	977	0.61	596	0.50	2420	0.62
nF + FA	7.0 + 0.1	1491	0.80	2198	0.82	1809	0.99	5498	0.87
nF + AA	7.0 + 0.1	786	1.02	1004	1.29	1020	1.18	2810	1.17
nF + HA	7.0 + 0.01	1263	1.03	1466	0.68	852	0.70	3680	0.79
mutation control	—	—	—	—	—	—	—	2584	0.15

[1] number of chromosomes tested. — [2] percentage of sex-linked lethals found.

abbreviations:

aF = acid formaldehyde
nF = neutral formaldehyde
FA = formic acid
AA = acetic acid
HA = hydrochloric acid.

All mutation frequencies are significant at the $p < 0.001$ level when compared with the non-treated control.

Table 34. Formic Acid-induced Mutations in Drosophila Melanogaster, Larval Feeding Experiments A (450)

treatment		brood							
substance	concentration	1st		2nd		3rd		total	
	%	n[1]	%[2]	n	%	n	%	n	%
nF	0.025	910	0.77	717	1.40	737	0.68	2364	0.93
nF	0.05	1266	1.26	1503	0.33	1601	0.31	4370	0.59
nF	0.025	1287	0.70	1213	0.91	1089	0.73	3589	0.78
nF	0.05	754	1.06	802	1.75	901	0.78	2457	1.18
FA	0.1	786	1.15	522	1.34	571	0.88	1879	1.11
AA	0.1	981	0.61	1307	0.60	1157	0.43	3445	0.54
HA	0.01	757	0.40	968	0.75	800	0.50	2225	0.55
nF + FA	0.025 0.1	839	0.95	857	1.17	587	1.19	2283	1.09
nF + FA	0.05 0.1	981	1.33	1352	0.96	1574	0.76	3907	0.97
nF + AA	0.025 0.1	716	0.98	782	1.28	652	0.77	2150	1.02
nF + AA	0.05 0.1	770	0.91	940	1.79	1092	1.10	2702	1.25
nF + HA	0.025 0.01	478	1.05	594	1.18	548	0.91	1620	1.05
nF + HA	0.05 0.01	446	2.02	544	1.95	447	1.12	1407	1.71
Mutation control	—	—	—	—	—	—	—	2584	0.15

[1] number of chromosomes tested. — [2] percentage of sex-linked lethals found.

[3] abbreviations:

nF = acid formaldehyde
nF = neutral formaldehyde
FA = formic acid
AA = acetic acid
HA = hydrochloric acid.

All mutation frequencies are significant at the $p < 0.001$ level when compared with the non-treated control.

Table 35. Formic Acid-induced Mutations in Drosophila melanogaster, Larval Feeding Experiments B (450)

substance	concentration	pH of the medium	tested chromosomes	mutations found	mutation frequency
nF	0.025%	7.5	398	0	0.00%
nF	0.05%	7.5	366	1	0.27%
FA	0.1%	7.5	544	2	0.38%
Mutation control	—	7.0	2584	4	0.15%

For these experiments a special prepared medium of pH > 7 was used (see "Materials and Methods"). Only the 2nd brood was analyzed. Concentration of the glycine-NaOH buffer: 0.1 M. The mutation frequency shows no significant deviation from the (untreated) control (0.15%) in contrast to the results obtained by testing the same substances in an acid medium.

Chemical analysis indicated that the sodium formate administered was completely eliminated, apparently by oxidation, by the 10-12 day of hatching. Survival rates and final embryo weight were essentially the same for both treated and control eggs. No qualitative or quantitative differences in malformations between treated and control embryos were noted. On the other hand, hydrocortisone, included in the study as a positive teratogenic control compound, at a level of 0.025 mg per egg, caused a highly significant increase in malformations in comparison with the controls.

D. Mice

In a study of the correlation between induction of epidermal hyperplasia and tumor development, Frei et al. (142) painted the ears of inbred male Swiss mice (six to ten weeks of age), ten per group, with 8% formic acid in distilled water, twice weekly for periods of 2, 5, 10, 20, and 50 days. At the end of each painting period, all animals were sacrificed, the ears removed, fixed in formalin, and embedded in paraffin. Sections were then cut, stained with hematoxylin and eosin, and examined for increased epidermal cell number (hyperplasia); for variation in thickness of epidermis; and for the presence of an inflammatory exudate. Untreated controls were included in each test. The data were analyzed statistically using the t test. No statistically significant histologic changes resulted.

BIOCHEMICAL ASPECTS

I. Breakdown

Very little information was found in the literature concerning breakdown of formic acid or formates spontaneously or in plants. Formic acid is reported to deteriorate somewhat in normal storage, creating a hazard. Ethyl formate is less stable; it decomposes when dissolved in water.

In sheep, formic acid is rapidly broken down to methane and carbon dioxide by rumen bacteria (482). In man also, part of the formic acid ingested in foods may be dissimilated by microorganisms of the intestinal tract (491).

II. Absorption-Distribution

Formic acid is absorbed from the gastrointestinal tract, through the lungs, through the intact skin, and from the urinary bladder. Ethyl formate is absorbed through the lungs and from the gastrointestinal tract; absorption through the intact skin has not been proven (271,491). Sodium formate is rapidly absorbed from the stomach. Ten minutes after oral administration of 4.44 grams to a human subject, 11.8 mg/100 ml of formic acid was found in the plasma (277). Formic acid, on entering the blood stream, is immediately transformed into sodium formate (277).

Absorbed formic acid is apparently oxidized, partly excreted unchanged in the urine, and partly metabolized in the tissues (491). Retained formate is rapidly utilized in the formation of proteins, lipids, and nucleic acids (370). These in turn are distributed throughout all tissues of the body. Following injection of C^{14} labeled sodium formate, fats from the testes, lungs, spleen, heart, and kidneys had the highest concentration of C^{14}; depot fats and spinal cord had the lowest. Among the tissue proteins, the greatest amounts of C^{14} were found in the stomach, spleen, kidneys, teses, and liver (434).

III. Metabolism and Excretion

A. Oxidation

The oxidation of formic acid in the organism is affected by several factors such as species, concentration, and certain vitamin deficiencies (105,491). Small doses administered to experimental animals usually are oxidized almost completely whereas 50% or more of larger amounts may be excreted in the urine.

The mechanism of formate oxidation, in rat liver and jejunum at least, involves a catalase-hydrogen peroxide complex and enzymes responsible for H_2O_2 formation, such as xanthine oxidase, uricase, monoamine oxidase, and D-amino acid oxidase (331). In folic acid deficiency, formic acid is not metabolized properly and an increased amount is excreted in the urine (197, 363). Vitamin B_{12} also plays a role in the oxidation of formate; a deficiency increases formic acid excretion but less so than a folic acid deficiency (320,447). The liver appears to be the main site of formic acid oxidation. Intestinal mucosa, spleen, kidneys, lungs, and blood also oxidize formate. Erythrocytes (frog, chicken, dog, human) also oxidize formic acid aerobically to carbon dioxide by means of the catalase-peroxide complex. In the erythrocyte, peroxide is supplied from a non-enzyme oxidation of certain sulfhydryl compounds like glutathione, homocysteine, and cysteine (371).

The biological half-life of formic acid in various species, according to Malorny (275,277), are given in Table 36.

Table 36. Biological Half-life of Formic Acid in Various Species (275,277).

Species	Biological Half-life (minutes)
Rats	12
Guinea-pig	22
Rabbit	32
Cat	67
Dog	77
Man	45 - 46

B. Excretion

1. Rats

Sperling (434) injected male Osborne-Mendel rats, 12-18 months of age, weighing 400-537 grams, intraperitoneally with a single dose of C^{14}-labeled sodium formate (0.07 - 0.10 mc) in a study of the comparative distribution and excretion of C^{14}-labeled carbonate and formate in the species. Approximately 80% of the injected dose was excreted over a period of 24 hours.

2. Rabbits

a. Lund (272) injected two full-grown male rabbits, weighing 3150 and 3300 grams, subcutaneously with single doses of sodium formate, 317 and 303 mg/kg BW, respectively. He determined the blood level, rate of formic acid excretion, and toxic effects over a period of 48 hours. One animal was maintained on an acid-forming diet (oats and water); the other on an alkalizing diet (turnips). The results are presented in Tables 37 and 38.

The author concluded from the data obtained that the rabbit is able to oxidize formic acid almost quantitatively and that alkalotic animals excrete larger amounts than acidotic animals.

b. Bastrup (041) injected one rabbit, 2700 grams BW, (strain, age, and sex not given), intramuscularly with formic acid, three doses of 550 mg each, at 24-hour intervals and determined the amount of formic acid excreted in the urine at regular intervals, as well as toxic effects, over a period of 4-5 days.

The animal tolerated 1650 mg of formic acid in divided doses over a period of two days without any apparent ill effects. Approximately 12% of the acid injected was excreted in the urine. Five days following the first injection, the urine level had returned to normal.

c. von Oettingen (491) reported results of an early study in rabbits where the urinary excretion was 14-19% following doses of one g/kg BW.

3. Dog

a. Lund (271) injected a full-grown male dog, 10.1 kg BW, (strain, sex and age not given) subcutaneously with 198 mg/kg BW of sodium formate and determined the blood level and amount of formic acid excreted over a 27-hour period. The animal was observed also for toxic effects. Results obtained are presented in Table 39. The data obtained revealed that 58% of the sodium formate injected was oxidized and 42% was excreted unchanged in the urine.

Table 37. Rabbit No. 2360, Weight 3150 g. Oct. 16, 10 o'clock; subcutaneous Injection of 10 ml 10% Solution of Sodium Formate (~676 mg formic acid). Diet during the Experimental Period: Turnips (272)

Hours aft. Injection	Diuresis ml	Formic acid excret.		Formic acid in blood mg/100 ml	pH
		mg/100 ml	mg total		
3	—	—	—	20	—
4	100	36.8	36.8	16	8.24
10	115	5.5	6.3	10	8.54
23	250	3.0	7.5	—	8.43
32	190	1.4	2.6	—	8.15
48	65	1.0	0.7	—	8.41

Total excretion: *53.9 mg formic acid.*

Table 38. Rabbit No. 1. Weight 3300 g. Oct. 19, 11 o'clock; Subcutaneous Injection of 10 ml 10% Solution of Sodium Formate (~ 676 mg formic acid). Diet during the Experimental Period: Oats (272)

Hours aft. injection	Diuresis ml	Formic acid excreted		Formic acid in blood mg/100 ml	pH
		mg/100 ml	mg total		
—	60	3.2	2.2	—	7.58
—	15	—	—	—	6.21
0	40	—	—	—	5.67
1	—	—	—	48	—
3	10	81.3	8.1	21	5.48
9	10	17.9	1.8	< 10	5.07
26	50	3.8	1.9	—	5.46
46	55	2.1	1.1	—	5.02

Total excretion: *12.9 mg formic acid.*

In a second experiment, a single dose of 100 mg/kg BW of sodium formate injected into the washed, empty bladder through a catheter tube, was reabsorbed over a 5-hour period. Preliminary experiments revealed that when sodium formate was given orally, 42% to 56% was excreted unchanged in the urine.

Table 39. The Excretion of Formic Acid after Subcutaneous Administration of Formic Acid

Dog. "H" Weight 10.1 kg. Oct. 30, 10 o'clock: Subcutaneous Injection of 40 ml of a 5% solution of sodium formate ($\sim$ 1.35 g formic acid). (270)

Hours after injection	Diuresis ml	Formic acid in urine		Formic acid in blood mg 100 ml
		mg/100 ml	mg total	
0	2	--	--	--
1	--	--	--	14.2
3.7	48	720	345	15.5
9.5	46	466	215	8.1
23	148	7.5	11	--
27	22	0.0	0.0	--

Total excretion: 0.571 g formic acid.

b. von Oettingen (491) reviewed early studies where following oral administration to dogs of 20, 5, and 1 gram of formic acid, 26%, 65%, and 8% to 9%, respectively, was excreted unchanged in the urine.

4. Man

von Oettingen (491) reports that of 20 grams of sodium formate taken per os by human subjects over a period of two days, 18% was excreted unchanged in the urine. Following an intravenous injection of four grams, 25 to 50% was excreted.

Formic acid is also a normal constituent of human urine of individuals on a mixed diet. Amounts ranging from 13 to 120 mg excreted per day have been reported (156,277).

C. Intermediary Metabolism

The participation of the formate ion in intermediary metabolism is well established (011,156). According to Rappoport (370), "formate is a precursor of serine, methionine, cysteine, purines, and ultimately becomes incorporated, in the form of these precursors, into proteins and nucleic acids". In newborn rats, formate is rapidly metabolized in the formation of proteins, lipids, and nucleic acids. Uptake of C^{14}-formate was found to be high early in life but decreased with age. More formate was incorporated into RNA than into DNA. Black et al.(056) found that there was actually a "preferential utilization" of formate for the synthesis of milk proteins. Fifty percent of C^{14}-labeled formate transferred to milk products was found in the casein.

Annison (011) points out that formate is incorporated into carbohydrates also via glucose by virtue of its being a precursor of the glucogenic amino acid serine involving activation by reaction with tetrahydrofolic acid.

Sperling (434) found that in rats injected intraperitoneally with C^{14}-labeled sodium formate, the retained C^{14} was distributed throughout all tissues of the body.

According to Black et al.(056), although only very small amounts of formate are ingested with foods, many compounds contribute to the C_1 pool for formation of endogenous formate. Serine, glycine, histidine, methionine, choline, and acetone were found to contribute carbon for the synthesis of formate in the rat. Also, other amino acids that give rise to the formation of ketone bodies, such as tyrosine, phenylalanine, or leucine, are potential sources of formate carbon through acetone formation. The liver appears to be an important site of formate metabolism.

Gley et al.(156) also point out that endogenous formic acid is formed through the metabolism of certain amino acids, especially histidine. Glutamic acid, formic acid, and ammonia are produced as these are metabolized in the liver.

Wheeler et al.(506) have outlined the important steps in formate metabolism in their report on the metabolism of normal rat liver and hepatomas (see Fig. 9)

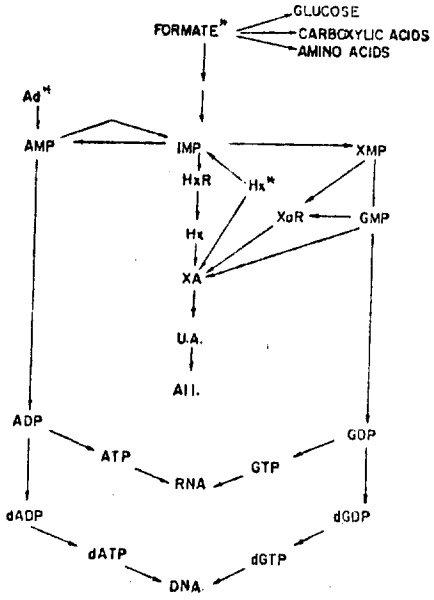

Figure 9. A Simplified Flowsheet of the Metabolism of Formate, Adenine, and Hypoxanthine (506)

Key

Ad	-	Adenine	IMP	-	Inosinic acid
AMP	-	Adenylic acid	HxR	-	Inosine
ADP	-	Adenosine diphosphate	Hx	-	Hypoxanthine
ATP	-	Adenosine triphosphate	Xa	-	Xanthine
GTP	-	Guanosine triphosphate	UA	-	Uric acid
GDP	-	Guanosine diphosphate	All.	-	Allantoin
GMP	-	Guanosine monophosphate	XaR	-	Xanthosine

The metabolism of C_1 compounds, formate and formaldehyde, in a wide variety of plants and animals, is controlled by folic acid (197). In the folic acid-deficient animal, formic acid is metabolized poorly and large amounts are excreted unchanged in the urine (185,363). On the other hand, in cells with an elevated level of this growth factor, there is an increased incorporation of formate into nucleic acids (197).

Vitamin E deficiency in the monkey also causes a derangement in formate metabolism (105). Severe deficiences lead to a nutritional muscular dystrophy with anemia and leucocytosis. In this condition there is an increased incorporation of formate into the DNA of skeletal muscle and bone marrow. Vitamin E deficiency does not affect its incorporation into proteins or into nucleic acids to tissues other than the bone marrow or skeletal muscle.

Ascorbic acid deficiency also affects formate metabolism by depressing utilization of formate in the synthesis of serine by 78% and in that of methionine by 85% (320).

According to von Oettingen (491) "the fate of ethyl formate in the organism and its excretion have evidently not been studied."

IV. Effects on Enzymes and Other Biochemical Parameters

Formic acid has an inhibitory effect on certain enzymes in vivo as well as in vitro. Lysozyme, ribonuclease, and trypsin are inactivated (423). Amounts as low as 6 mg/kg BW in the rabbit cause a persistent methemoglobinemia which appears to be due to the action on catalase. On the other hand, gastric secretion and peristalsis are stimulated by formate (491).

von Oettingen (491) has reviewed the literature pertaining to the physiologic effects of formic acid and formates. The nervous system apparently is especially susceptible to the action of formate. In mice, 1 ml of a 2.5% solution of formic acid intrarectally slowed respiration and caused dyspnea, paralysis and death. A dose of 0.46 gm/kg formic acid in the rabbit intravenously depresses the CNS; larger doses caused convulsions. Fatal doses cause clonic, and sometimes tonic convulsions, progressive dyspnea, and paralysis of the medulla. In cats, 400 mg/kg of sodium formate subcutaneously produced somnolence. Larger doses caused staggering and death in about 3 hours. Dogs manifested a staggering gait and weakness lasting 24 hours following subcutaneous administration of 800 mg/kg of sodium formate. Fatal doses intravenously caused clonic convulsions, progressive dyspnea and paralysis of the medulla.

Formic acid at a concentration of 1:1,000,000 has a light stimulating effect on the isolated frog heart, causing a slight increase in amplitude and heart beat. Concentrations as low as 1:10,000, however, quickly and irreversibly arrest heart action (491).

In vivo, formic acid also causes injury to the myocardium that is directly proportional to the dose. The main symptoms are "moderate primary increase and subsequent progressive decrease of the systole, slowing of the heart beat, contraction irregularities, arrhythmias and diastole arrest" (491). Formic acid is considered by some authorities to be seven times more toxic on heart action than formaldehyde, and 187 times more toxic than methanol (491).

With regard to the vascular system, formic acid intravenously causes immediate vasoconstriction. Sodium formate, on the other hand, causes vasodilation in the liver, brain, and kidney but vasoconstriction in the limbs. In the frog, trace amounts of formic acid (1:1,000,000) cause slight vasodilation; dilutions as high as 1:500,000 produce vasoconstriction; and a concentration of 1:1000 causes complete blocking of the circulation. There is a rise in the blood pressure due to intravenous formic acid during vascular constriction; larger doses, however, have a hypotensive effect (491).

Formic acid stimulates gastric secretion and peristalsis and enhances absorption of protein from the intestinal tract. It also exerts a diuretic effect but is less active in this respect than theobromine. Single large doses, or repeated small doses of formate cause kidney injury. Rabbits are the most susceptible of the experimental animals. Diet appears to play a role since animals on an acid diet are more susceptible than those on green foods (491).

Formic acid is reported to possess strong germicidal properties with dilutions as high as 1:50,000 to 1:100,000 being effective against some microorganisms. Concentrations of 60 mg/liter prevent the growth of *Bacillus anthracis* and *B. pyocyanus.* Yeasts, however, are somewhat more resistant, concentrations of 0.2% being required to prevent growth and fermentation. Germicidal action is believed to be due to the un-ionized molecule (491). Formic acid has been used in certain countries as a food preservative (137). Berard *et al.*(051) report that a formic acid (20%) colloid of methylolmelamine (17%) prevents microbial deterioration of cotton at a level of 12% resin add-on.

Methyl, ethyl, and isopropyl formates are effective against various life cycle stages of the dried fruit beetle, raisin moth, and other insects that infest dried fruits, nuts, cereals, and tobacco. These compounds are used in this area of the food industry as fumigants (018,139,485,491).

Biehl (054) states "ants have been used in therapy since antiquity". Alcoholic extracts and boiled mixtures of whole ants containing formic acid as the active principle have been used as rubbing ointments, in baths, and also in internal medicine. Depression, melancholia, and nervous weakness (vegetative dystonia) were treated as long as 1000 years ago in this way. Later, these natural concoctions were replaced with synthetic formic acid preparations. Doses of sodium formate as high as three to four grams per day have been used (156). Today, the use of formic acid in medicine is limited mainly to primarily allergic diseases, particularly asthma (non-cardiac type), eczema, psoriasis, urticaria, hay fever, exudative diathesis, rheumatic disease, many types of migrane, pregnancy vomiting, mucitis of the gastrointestinal tract, and chronic kidney inflammation. Unfortunately, treatment for a long time is usually required. Some patients develop hypersensitivity to the compound. Conditions in which large doses of formic acid should not be used are hypertonia, coronary sclerosis, and angina pectoris (054).

Eisenstadter (121) reported good results in the treatment of inflammatory and tumor diseases of the female genital organs with formic acid administered intravenously in doses of 1 ml of a 1:1,000,000 solution every 10 - 14 days for periods up to 10 weeks. In a few acute and subacute cases, doses ten times stronger were safely used.

Meiselas (292) stated that formic acid alone, or in combination with silicic acid and cobra venom (Nyloxin) had no better effect than an inert control substance in alleviating pain in a double-blind study with twenty-nine osteoarthritis patients.

Formic acid and sodium formate have been used as strong caustic astringants and counter-irritants (438).

V. Drug Interaction

Folic acid antagonist drugs, such as methotrexate, inhibit the metabolism of formic acid resulting in increased amounts being excreted unchanged in the urine (275).

VI. Consumer Exposure Information

Formic acid occurs naturally in a number of food plants, fruits, fruit juices, and wines as well as in milk, cheese, meat, certain vegetables, and some mineral waters (056,146,275,289,303).

In the food industry, formic acid finds use as a flavor adjunct in ice cream, ices, candy, baked goods and some other foods. Concentrations up to 18 ppm are used in certain types of candy (139). Usage levels for a number of other food categories are shown in Table 40. Possible daily intake values for various age groups are shown in Table 41. The amount of formic acid imported has declined steadily from more than three million pounds in 1965 to less than 1/4 million pounds in 1972 (See Table 42) (469). Annual poundage data are given in Table 43.

Formic acid is permitted as a preservative for silage in an amount not to exceed 2.25% of the silage on a dry-weight basis or 0.45% when direct cut. The silage should not be fed to live-stock until four weeks after treatment (020).

Ethyl formate occurs naturally in certain fruits, fruit juices, wines, rum, and some other distilled alcoholic beverages. Oranges, apples, pears, honey, orange juice, and coffee extract are typical fruits and beverages where this compound is found (146).

In the food industry, ethyl formate is used as a component of many flavorings, such as, blueberry, raspberry, strawberry, butter, butterscotch, apple, apricot, banana, cherry, grape, peach, plum, pineapple, tutti fruiti, brandy, rum, arrack, sherry, and whiskey (139). It is used in chewing gum, candy, ices, ice cream, baked goods, and a number of other foods (see Table 40). Possible daily intakes range from 0 to 83.7 mg. (Table 41). Total 1970 poundage reported to NAS and FEMA was 29,077 pounds (see Table 43). Ethyl formate is used also as a bulk and package fumigant (fungicide and larvacide) for certain dried fruits, nuts, dry cereals, and tobacco (018,139,491). With raisins and dried Zante currants, the maximum concentration permitted in the final product is 250 ppm (018).

Formic acid and sodium formate are included in the category of substances possibly migrating to foods from paper and paper board food containers (019).

Acceptable daily intake levels (ADI) for formic acid and ethyl formate are 0-5 mg/kg BW (conditional), for each, calculated as total formic acid from all food additive sources (515,516). Maximum allowable concentrations per 8-hour workshift are 9 mg per cubic meter of air for formic acid and 300 mg per cubic meter of air for ethyl formate (016).

Table 40. Comprehensive GRAS Survey Usage Levels (138)

Substance Name	Food Category	Usual Use WTD Mean%	Max. Use WTD Mean,%
Formic Acid *	Baked Goods (R)	1.912903	5.745161
	Frozen Dairy (R)	1.006897	4.331034
	Soft Candy (R)	1.903448	4.968966
	Gelatin pud (R)	0.481481	3.402778
	Bev Typ I(R)	0.826667	0.885593
	Bev Typ II (R)	1.000000	3.000000
	Hard Candy (R)	6.000000	6.000000
	Misc. Unclas.	0.900000	2.733333
Ethyl Formate **	Baked Goods (R)	0.02752	0.02966
	Frozen Dairy (R)	0.00923	0.01020
	Meat Prods (R)	0.00025	0.00100
	Soft Candy (R)	0.01745	0.01838
	Gelatin Pud (R)	0.00923	0.01495
	Bev Typ I (R)	0.00478	0.00550
	Bev Typ II(R)	0.00019	0.00038
	Hard Candy (R)	0.01158	0.01158
	Chewing Gum (R)	0.00915	0.01479
	Misc. unclas.	0.00887	0.05738

* From: Table 4, Usage Levels Reported for FEMA Questionnaire, Substances Not in NAS Appendix (Group III) Regular Foods Only

** From: Table 2, Usage Levels Reported for NAS Appendix A Substances (Group I) Used in Regular Foods (R)

Table 41. Possible Daily Intakes of NAS Appendix A Substances (Groups I & II) Per Food Category and Total Dietary, Based on Food Consumption by Total Sample (138).

Substance name	Food category	No. Firms	Age Level	Possible Daily Intakes, mg. Ave.	High A	High B
Formic Acid	Baked goods		0-5 mo	0.006504	0.008608	0.019534
			6-11 mo	0.048588	0.099088	0.145927
			12-23 mo.	0.104253	0.171779	0.313111
			2-65+yr.	0.262450	0.389850	0.788236
	Frozen dairy		0-5 mo.	0.001007	0.004128	0.004331
			6-11 mo.	0.009566	0.026582	0.041145
			12-23 mo.	0.014499	0.034033	0.062367
			2-65+yr.	0.025777	0.062126	0.110874
	Soft candy		0-5 mo.	0.000381	0.003801	0.000994
			6-11 mo.	0.004188	0.012943	0.019320
			12-23 mo.	0.006662	0.017702	0.017391
			2-65+yr.	0.011040	0.033501	0.028820
	Gelatin pud		0-5 mo.	0.000963	0.001300	0.006806
			6-11 mo.	0.006163	0.018681	0.043556
			12-23 mo.	0.006644	0.016178	0.046958
			2-65+yr.	0.009822	0.025278	0.069417
	Bev Typ I		0-5 mo.	0.001984	0.002976	0.002125
			6-11 mo.	0.018765	0.064232	0.020103
			12-23 mo.	0.048005	0.134333	0.047999
			2-65+yr.	0.085973	0.229565	0.092102
	Bev. Typ II		0-5 mo.	0.000000	0.000000	0.000000
			6-11 mo.	. . . .	0.000100	. . . .
			12-23 mo.	. . . .	0.000200	. . . .
			2-65+yr.	0.032500	0.094400	0.097500
	Hard candy		0-5 mo.	0.000000	0.000000	0.000000
			6-11 mo.	0.000600	0.001800	0.000600
			12-23 mo.	0.001800	0.005400	0.001800
			2-65+yr.	0.003600	0.010200	0.003600
	All categories		0-5 mo.	0.010838	0.020819	0.033789
			6-11 mo.	0.087869	0.223427	0.262262
			12-23 mo.	0.178664	0.379625	0.489627
			2-65+yr.	0.431162	0.844910	1.190549

Table 41 (Cont'd)

Substance name	Food category	No. Firms	Age Level	Possible Daily Intakes, mg. Ave.	High A	High B
Ethyl formate	Baked goods	20	0-5 mo.	0.935680	1.238400	1.008440
			6-11 mo.	6.990080	14.255360	7.533640
			12-23 mo.	14.998400	24.712960	16.164700
			2-65+yr.	37.757440	56.085760	40.693520
	Frozen dairy	18	0-5 mo.	0.092300	0.378430	0.102000
			6-11 mo.	0.876850	2.436720	0.969000
			12-23 mo.	1.329120	3.119740	1.468800
			2-65+yr.	2.362880	5.694910	2.611200
	Meat prods		0-5 mo.	0.002750	0.007250	0.011000
			6-11 mo.	0.051750	0.139500	0.207000
			12-23 mo.	0.755000	0.129750	0.302000
			2-65+yr.	0.196000	0.325250	0.784000
	Soft candy		0-5 mo.	0.034900	0.349000	0.036760
			6-11 mo.	0.383900	1.186600	0.404360
			12-23 mo.	0.610750	1.622850	0.643300
			2-65+yr.	1.014000	3.071200	1.066040
	Gelatin pud.		0-5 mo.	0.184600	0.249210	0.299000
			6-11 mo.	1.181440	3.581240	1.913600
			12-23 mo.	1.273740	3.101280	2.063100
			2-65+yr.	1.882920	4.845750	3.049800
	Bev Typ. I		0-5 mo.	0.114720	0.172080	0.132000
			6-11 mo.	1.085060	3.714060	1.248500
			12-23 mo.	2.590760	7.767500	2.981000
			2-65+yr.	4.971200	13.274060	5.720000
	Bev Typ.II		0-5 mo.	0.000000	0.000000	0.000000
			6-11 mo.	. . . .	0.000190	. . . .
			12-23 mo.	. . . .	0.000380	. . . .
			2-65+yr.	. . . .	0.179360	0.123500
	Hard candy		0-5 mo.	0.000000	0.000000	0.000000
			6-11 mo.	0.011580	0.034740	0.011580
			12-23 mo.	0.034740	0.104220	0.034740
			2-65+yr.	0.069480	0.196860	0.069480
	Chewing gum		0-5 mo.			
			6-11 mo.	0.009150	0.009150	0.014790
			12-23 mo.	0.009150	0.027450	0.014790
			2-65+yr.	0.018300	0.036600	0.029580
	All categories		0-5 mo.	1.364950	2.394370	1.589200
			6-11 mo.	10.589810	25.357560	12.302470
			12-23 mo.	20.922160	40.586130	23.672430
			2-65+yr.	48.332070	83.709750	54.147120

Table 42. U. S. Imports of Formic Acid (469)

Year	Net Quantity (lbs)
1965	3,219,943
1966	3,306,947
1967	
1968	2,011,831
1969	272,808
1970	407,199
1971	407,002
1972	189,251

Table 43. Annual Poundage Data for NAS Appendix A Substances (Groups I & II) (138)

Substance Survey No.	# Reptd. to NAS 1960/1970	Poundage Reptd. NAS (Match. Repts. Both yrs) 1960	1970	Total 1970 Poundage Reptd. NAS	# Repts. to FEMA	Poundage Reptd. FEMA 1970 only	Total 197 Poundage Reported NAS+FEMA
Ethyl formate NAS 0079 FEMA 2434	*/*	33	33	33	56	29,044	29,077
Formic acid FEMA 24870	5					128	128

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